UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

+ + +

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

+ + +

GENERAL AND PLASTIC SURGERY DEVICES PANEL

+ + +

August 30, 2011
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, MD 20877

PANEL MEMBERS:

JOSEPH LoCICERO III, M.D.	Chair
A. MARILYN LEITCH, M.D.	Voting Member
SUSAN GALANDIUK, M.D.	Voting Member
DELORA L. MOUNT, M.D.	Voting Member
MARY H. McGRATH, M.D., M.P.H.	Voting Member
NANCY N. DUBLER, LL.B.	Temporary Non-Voting Member
JASON T. CONNOR, Ph.D.	Temporary Non-Voting Member
MARGARET A. HONEIN, Ph.D.	Temporary Non-Voting Member
SEAN HENNESSY, Pharm.D., Ph.D.	Temporary Non-Voting Member
LEONARD M. GLASSMAN, M.D.	Temporary Non-Voting Member
LEIGH F. CALLAHAN, Ph.D.	Temporary Non-Voting Member
BARBARA I. CROUCH, Pharm.D.	Temporary Non-Voting Member
ELBERT B. WHORTON, JR., Ph.D.	Temporary Non-Voting Member
ELIZABETH C. JONES, M.D., MPH	Temporary Non-Voting Member
MARLENA VEGA, M.S.W., Ph.D.	Patient Representative
MICHAEL G. HALPIN	Industry Representative
KRISTINE R. MATTIVI, M.S.	Consumer Representative
JAMES P. SWINK	Designated Federal Officer

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

FDA REPRESENTATIVES:

MARK MELKERSON, M.S.
Director, Division of Surgical, Orthopedic, and Restorative Devices
Office of Device Evaluation

DANICA MARINAC-DABIC, M.D., Ph.D.
Director, Division of Epidemiology
Office of Surveillance and Biometrics

ERICA JEFFERSON
Press Contact

FDA PRESENTERS:

CARA J. KRULEWITCH, CNM, Ph.D., FACNM
Branch Chief, Division of Epidemiology
Office of Surveillance and Biometrics

OZLEM TOPALOGLU, Ph.D., M.P.H.
Division of Epidemiology
Office of Surveillance and Biometrics

FDA ADVISORS:

PHYLLIS SILVERMAN, M.S.

SPONSOR PRESENTERS (ALLERGAN):

RUI AVELAR, M.D.
Chief Medical Officer
Allergan, Inc.

SPONSOR ADVISORS (ALLERGAN):

ROSE MONROE
SCOTT SPEAR, M.D.

SPONSOR PRESENTERS (MENTOR):

JOHN CANADY, M.D.
Medical Director, Mentor Worldwide, LLC

ROGER WIXTROM, Ph.D., DABT-LSCI

SPONSOR ADVISORS (MENTOR):

NICOLA SELLEY
GENE POGGIO, Ph.D.

OPEN PUBLIC HEARING SPEAKERS:

DIANA ZUCKERMAN, Ph.D.
BRENDEL FRANCE DE BRAVO on behalf of KATHY NYE, PAM NOONAN-SARACENI, and ANNE STANSELL
LINDA MACDONALD GLENN, J.D., LL.M.
BENJAMIN A. GITTERMAN, M.D.
BETTYE GREEN
CHERYL LEEMAN
JULIANA STEBBINS on behalf of JUDY McCAUL
SUSAN WOOD, Ph.D.
NICOLE NOLL
JANICE ERICKSON
JUDITH FAUCETTE on behalf of JANE THOMPSON
SUSAN O. CASSIDY, M.D.
MARGARET DUNKLE
EDWARD P. MELMED, M.D.
JEFFREY KENKEL, M.D.
CAROLYN WOLF
LAURIE CASAS, M.D.
WILLIAM P. ADAMS, JR., M.D.
JEAN SILVER-ISENSTADT, M.D., Ph.D.
SUSAN DORSEY and PETE DORSEY
CYNTHIA ANNE MASON
CYNTHIA A. PEARSON
GLORIA DUDA, M.D.
ROBERT S. HAMAS, M.D.
SUE DORFMAN on behalf of CHELSEA C.

INDEX

INDEX (cont.)

INDEX (cont.)

M E E T I N G

(8:05 a.m.)

DR. LoCICERO: I'll call this meeting of the General and Plastic Surgery Devices Panel to order.

I am Dr. Joseph LoCicero. I am a general and thoracic surgeon and Professor Emeritus of Surgery at SUNY Downstate.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda, the Committee will discuss and make recommendations on postmarketing issues related to silicone gel-filled breast implants, which are going to be referred to as SGBI, postapproval studies for SGBI, and a discussion of different innovative methodological approaches to the conduct of postmarket studies regarding SGBI. Additionally, the Panel will discuss key long-term safety issues associated with SGBI in the real-world setting for both the currently mandated studies and future studies for newly approved SGBIs.

Before I begin, I would like to ask our distinguished Panel members and FDA staff seated at the table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. I'm going to begin to my right.

MS. CROUCH: I'm Barbara Crouch. I'm a pharmacist and clinical toxicologist at the University of Utah College of Pharmacy and Executive Director of the Utah Poison Control Center.

DR. GLASSMAN: Leonard Glassman. I'm a diagnostic radiologist. I'm the American College of Radiology Breast Imaging Scientist at the AIRP. I'm the former head of breast imaging at BAFIP. I'm Clinical Professor of Radiology at G.W. And my day job is I'm in private practice of radiology in Washington, D.C.

DR. McGRATH: My name is Mary McGrath, and I am a practicing plastic surgeon and Professor of Surgery at the University of California, San Francisco.

DR. HENNESSY: Good morning. My name is Sean Hennessy. I do drug safety research at the University of Pennsylvania.

DR. GALANDIUK: My name is Susan Galandiuk. I'm a colorectal surgeon at the University of Louisville, where I'm a Professor of Surgery and Director of the Price Institute of Surgical Research.

DR. MOUNT: I am Delora Mount. I'm Associate Professor of Plastic Surgery at the University of Wisconsin in Madison, Wisconsin.

DR. VEGA: Hi. Marlena Vega. I'm a three-time, third-generation survivor of cancer, and I'm a psycho-oncologist. I practice in the Bronx and Manhattan. And I founded with -- the organization called Sobrevivir, which is A Will to Live.

MS. MATTIVI: I'm Kris Mattivi. I'm a physical therapist and the Director of Analytic Services at the Colorado Foundation for Medical Care. I'm the Consumer Representative on this Panel.

MR. HALPIN: Good morning, I'm Mike Halpin. I'm the Vice President of Regulatory Affairs at Genzyme Corporation. I specialize in medical devices and cell and gene therapy products, and I will be acting as the Industry Rep today.

DR. LoCICERO: We're going to skip Mr. Swink and then go to my left.

DR. CALLAHAN: I'm Leigh Callahan. I'm a clinical epidemiologist and Professor of Medicine and Social Medicine at the University of North Carolina in Chapel Hill.

DR. HONEIN: I'm Peggy Honein. I'm an epidemiologist with expertise in maternal and child health epidemiology with the Centers for Disease Control and Prevention.

DR. LEITCH: Marilyn Leitch. I'm a surgical oncologist at UT Southwestern in Dallas. I'm Professor of Surgery and Medical Director of the Center for Breast Care.

DR. WHORTON: Hi, I'm Elbert Whorton, Professor of Biostatistics and Epidemiology at the University of Texas Medical Branch in Galveston, and Director of the Galveston National Laboratories for Biostatistics. I'm Associate Professor of Biostat in the Department of

Preventive Medicine and Community Health.

MS. DUBLER: I'm Nancy Dubler. I'm an attorney. I'm the Consultant for Ethics for the Health and Hospitals Corporation, a public hospital system in New York City, and Professor Emerita of Bioethics at the Albert Einstein College of Medicine.

DR. CONNOR: I'm Jason Connor. I am a biostatistician specializing in Bayesian adaptive clinical trial design for Berry Consultants and also have an appointment at the University of Central Florida's College of Medicine.

DR. JONES: Elizabeth Jones. I'm a radiologist. I am Director of Clinical Operations and Radiology at NIH Clinical Center.

DR. MARINAC-DABIC: Good morning, my name is Danica Marinac-Dabic. I'm a physician and epidemiologist and also Director of the Division of Epidemiology at CDRH.

MR. MELKERSON: I'm Mark Melkerson. I'm a biomedical engineer by training, and I'm the Director of the Division of Surgical, Orthopedic, and Restorative Devices at FDA's Office of Device Evaluation.

DR. LoCICERO: Thank you. If you have not already done so, please sign the attendance sheets that are on the tables outside of the doors.

Mr. Swink, the Designated Federal Officer for the General and Plastic Surgery Devices Panel, will now make some introductory remarks.

MR. SWINK: Good morning. I will now read the Conflict of

Interest Statement and the Temporary Voting Member Statement.

The Food and Drug Administration is convening today's meeting of the General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with the Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the Committee essential

expertise.

Related to the discussions of today's meeting, members and consultants of this Panel who are special Government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations on postmarketing issues related to silicone gel-filled breast implants. The discussion will include different innovative methodological approaches to the conduct of postmarket studies and key long-term safety issues associated with silicone gel breast implants in the real-world setting. This is a particular matters meeting during which specific matters related to silicone gel-filled breast implants will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208 and Section 712 of the FD&C Act. A copy of this statement will be available for review at the registration table during the meeting and will be included as a part of the official transcript.

Michael Halpin is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Genzyme Corporation.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue.

For the duration of the General and Plastic Surgery Devices Panel meeting on August 30th and 31st, 2011, Dr. Leigh Callahan, Dr. Barbara Crouch, Dr. Elizabeth Jones, Dr. Sean Hennessy, and Dr. Marlena Vega have been appointed as Temporary Non-Voting Members.

For the record, Dr. Callahan serves as a consultant to the Arthritis Advisory Committee of the Center for Drug Evaluation and Research. Dr. Crouch and Dr. Hennessy serve as consultants to the Drug Safety and Risk Management Advisory Committee for CDER. And Dr. Marlena Vega serves as a patient representative to the Oncology Drugs Advisory Committee for CDER. Dr. Elizabeth Jones serves as a consultant to CDER.

These individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

This appointment was authorized by Jill Hartzler Warner, J.D., Acting Associate Commissioner for Special Medical Programs, on August 29th, 2011.

Before I turn the meeting back over to Dr. LoCicero, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Incorporated. Their telephone number is (410) 974-0947.

The press contact for today's meeting is Erica Jefferson. There she is right there.

And I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the panel meeting has concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to the FDA, please arrange to do so with Ms. AnnMarie Williams at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

Finally, please silence your cell phones and other electronic devices at this time. Thank you very much.

DR. LoCICERO: Thank you. We will now have a brief Panel

update from Dr. Danica Marinac-Dabic.

DR. MARINAC-DABIC: Good morning, ladies and gentlemen, Mr. Chairman, Mr. Melkerson, distinguished Panel members, and members of the audience. My name is Danica Marinac-Dabic, and I direct the Division of Epidemiology at CDRH's Office of Surveillance and Biometrics.

The Division of Epidemiology is one of the four divisions in our postmarket office and is in charge of all mandated postmarket studies, whether those are being conducted as a part of the PMA authority or Section 522 authority.

In addition, we also are in charge of FDA-sponsored epidemiologic research that is designed to address methodological approaches on studying medical devices in the postmarket setting and synthesizing all available evidence to enrich the evidence-based regulatory decision making at CDRH.

As you know, postapproval studies are one of the postmarket tools that FDA utilizes in studying postmarket safety and effectiveness and continue the reliability of medical devices.

As you know, we often seek the input from the Panel members; your unique clinical expertise, and the scope and the prominence of your input, and your role in the FDA decision making is a matter of record. We continue to be deeply grateful for the time and effort you give to us in terms of your assistance and your advice in how to improve the studies both in the

premarket and the postmarket setting.

In addition to the postmarket studies that are conducted by industry, and in this diagram they're represented in red, CDRH postmarket science also encompasses many different dimensions. As you can see, there is a huge body of FDA-sponsored postmarket studies geared toward advancing the methods and infrastructure.

In addition to that, we also have evolving FDA-led initiatives, such as Sentinel or MDEpiNet, which stands for Medical Device Epidemiology Initiative, all geared toward addressing the public health needs, to the improvement of infrastructure methods for medical devices.

During the last several years, CDRH had spent a significant amount of resources and time to advance the Postapproval Studies Program. We established the integrated CDRH Postapproval Studies Program in 2005. And by integrated, I mean that there have been, since that time, much stronger communication and collaborative effort between our premarket and postmarket offices.

In 2005 we began raising scientific rigor for postapproval studies, and in 2006 we developed and instituted an electronic tracking system that tracks the progress of all postapproval studies. We also issued at that time, and updated several times after that, the postapproval study guidance and created the postapproval study website.

In 2007 we started updating, on a routine basis, the Advisory

Panel members on the progress of postapproval studies.

In 2008 we initiated BIMO inspections of postapproval studies. And as you can see, since 2008, we started focusing on broadening the more traditional postapproval study approaches towards more focus on infrastructure building, methodology development, strategic partnerships, and certainly wanted to take better advantage of the existing external data that FDA historically did not take advantage of.

We also believe, strongly believe, that the information that we gain in the postmarket setting has to be broadly available and valid. An important piece of that is our transparency initiative, in order to bring the data to the American public. Everything that is learned through these postapproval studies we would like to post onto our website.

So you can see on this slide that, for all ongoing studies, we now post detailed study protocol with the study population, sample size, study endpoints, data collection, and follow-up visits. For the studies that are completed, you can see the results of the study now on the web, available to the public to see, and also we point toward study strengths and limitations so the proper interpretation of the data can be conducted by the clinicians, by the public, by the patients.

This is our website. It's linkable to the PMA database and searchable, and we track every single study that is ordered by the FDA.

Now, I would like to briefly give you a postapproval studies

update.

As you can see, from 2005, these are the numbers of approved original PMAs and panel-track supplements. What you see in blue are the approved PMAs and panel-track supplements. What you see in red, represented on the graph, are the ones that had been approved with a condition of approval. So you can see that not for every PMA that we review and approve we require the postapproval study. But in the case when we do postapproval study requirements, we often issue more than one requirement per PMA. So we would have, sometimes, multiple studies issued for one PMA that is approved.

If you're interested to know how these studies are doing in terms of the progress, this slide captured the compliance for all of the 351 postapproval studies that have been issued so far for medical devices. Eighty-five percent of the studies are progressing well, and we call them progress adequate. For the 15 percent, there are still some issues with the progress of the studies, and we are working very closely with the manufacturers to bring those studies back on track. This number includes also the completed studies. So, you know, the number is slightly better than if we look at -- when we compare that with the ongoing studies.

For this slide I show -- if you look for the subset of the postapproval studies that had been issued post-2005, we see that approximately one-fifth of the studies are not progressing well.

When we examine what are the reasons for inadequate progress, you would see that a large number of those studies that are not progressing well have issues with the subject enrollment, also followed up by the lower follow-up rates. And anything that goes below 80 percent we qualify on our website as a study that's not progressing well. The site enrollment is also a reason for a small subset of those studies, and also sometimes there are missing data.

Not surprisingly, when we look at the study designs, the vast majority of the studies that we ask at the time of the approval are prospective cohort studies. But you can see that we also employ a number of other study designs.

In terms of the data sources, more and more we advocate for the use of registries for postmarket studies. However, you will see that only five percent of our postapproval studies are nested in the existing registries. Twenty-seven percent of the studies use the sponsor's registry, and all others use new data collection.

When we complete postapproval studies, we post the results on the web, and this represents the latest numbers from 2010 and 2011.

And this slide represents the labeling change requests that are based on the postapproval study final results, meaning that these studies really do have a public health impact, and we share the knowledge that had been gained with the public, with the clinical community, with all interested

stakeholders.

If we look specifically for the studies that fall into your area of expertise and interest, this is how the number looks like. You see there is a substantially smaller, lower number of studies that have been requested since 2005 in this particular clinical area of expertise.

And these are the individual study requirements. Again, all of these studies do mirror the studies that I presented for overall, so I'm not going to go into a lot of details.

In terms of the compliance, 23 percent of the studies from general and plastic surgery devices are classified as non-adequate progress; the vast majority of them are progressing well.

In terms of the design of these studies, again, the large number of those are again prospective cohort studies.

And we don't have any external registries being utilized, so far, for a postapproval study mandate. All of the studies fall into the new data collection, meaning that the sponsors are generally patient to meet the postmarket requirements.

Follow-up rates are the primary reason for studies being classified as progressing non-adequately.

And in the next five minutes I'm going to walk you through some very latest initiatives that FDA had launched during the last few years, that we hope are going to be very innovative in the way of how we think

about postapproval studies, exploring new infrastructure and new methodologies that can be potentially used to meet postmarket study requirements.

As I mentioned, we recognize the value of the registries as a data source and, historically, FDA had not been engaged in the efforts outside of the FDA, in terms of development of the registries and utilization of the registries for postmarket.

However, I have listed here the recent efforts during the last several years that fall into categories of, you know, using existing registries for postapproval studies and surveillance. These are some good examples, great examples, actually. From the cardiovascular world, INTERMACS Registry, or from the orthopedics world, Total Joint Replacement Registry -- actually Kaiser national registry -- and Australian National Joint Replacement Registry.

And we were successfully able to nest the required postmarket studies in those registries, meaning that we're getting the data directly from the registry, working with our colleagues from industry to making sure that the data that are in the approval order are collected using those registries.

FDA also facilitates new registry development, and you will see us in a lot of conferences, clinical conferences, talking about a need for these registries, working closely with the societies. I listed just a number of those on the slide, such as our work with ACC, HRS, STS; also with the AAOS on the

American Joint Replacement Registry. We have a number of efforts in the diagnostic and therapeutic bronchoscopy arena, urogynecological efforts, and also with ACC on the IMPACT Registry.

We also use existing registries for discretionary studies, meaning that when FDA sponsors a study, we utilize those registries. I'm not going to go into the details of these, but you will have these handouts for the future reference.

We explore capabilities of the registries for active surveillance; again, an important method to advance our existing spontaneous surveillance, where we're trying to pilot some of the innovative methods for active surveillance and also to link the studies from the registries with the administrative claims data to help us study medical devices because, as you know, currently we do not have unique device identification, so identifying a specific brand of devices is not always easy in claims data. We also advocate for registry -- on the AHRQ's guidebook on registries. We also build methodological infrastructure for registries.

In terms of the methodological work, we have recently published the evidence appraisal for medical devices, a framework, through our collaborative work with Harvard and Cornell.

We also are looking into using Bayesian methodologies more to make better use of existing data that we have in the premarket and postmarket setting, and to figure out how we cannot dismiss not-so-perfect

data that's sitting in, very often, historically, silos of information in the premarket and postmarket; but rather, how we can combine that data to have the CDRH the best available data at any time in the device cycle to make the best decisions.

And, again, this is one of the recently published papers from our group that is piloting on the hip arthroplasty devices using the innovative methods of combining data from disparate data sources.

And, finally, my concluding slides focus on strategic partnerships. FDA cannot do this job alone. We rely on our stakeholders, clinical community experts, such as advisory panel, you know, payers, industry, colleagues, patient input, to do our job better.

We have recently launched Medical Device Epidemiology Network, or we call that for short MDEpiNet Initiative, which was specifically geared toward advancing the methods for devices. Lots of work in the Agency is sponsored and done from pharmacopeia, and we felt it's time now to launch an initiative that will focus specifically for procedures, surgical devices, implantable devices, aesthetic devices, to figure out what are the gaps, how we can improve the surveillance and studies.

So these objectives are listed on the slide, and we definitely are marching toward, you know, establishing the public-private partnership that will work -- that will establish the collaborative work between the FDA and academic centers and other stakeholders. This is our logo.

And basically how this is going to work, you know, FDA epidemiologists will work very closely with the epidemiologists and other clinical experts from MDEpiNet sites. This is going to be, in the first phase, done through the contracting work. After that it's going to be done through the public-private partnership, meaning that that's going to be our external arm of expertise that we're going to be using routinely in our evidence synthesis, in comparative effectiveness research, advancing methodologies that will focus for medical devices. And these are some of the tools that we hope are going to come out of this effort.

Basically, that would be the end of my talk; expect that I would like you to mark the following dates for the very interesting conferences that we are sponsoring next year. The first, in December, will focus on methodologies for surgical devices; the one in March on 522 studies; in April on MDEpiNet conference, annual conference; in May on a conference on postapproval studies; and in June we're going to be having again a public conference on registries for regulatory science.

I thank you very much for your attention, and I wish you a successful two days. Thank you.

DR. LoCICERO: Thank you, Dr. Marinac-Dabic.

We will now proceed with today's agenda. We have a 15-minute introductory presentation followed by a 45-minute discussion on current PAS studies.

I'd like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

Dr. Krulewitch, you may begin.

DR. KRULEWITCH: Good morning, distinguished Panel and guests. I am Dr. Cara Krulewitch. I am a nurse midwife and epidemiologist and Branch Chief in the Division of Epidemiology in the Office of Surveillance and Biometrics.

I will begin by setting the framework for presentations and discussions that will follow and then provide you with an update on the postapproval studies that are current.

The purpose of this meeting is to update the Panel on the status of ongoing postapproval studies and to discuss strategies to evaluate the real-world and long-term performance of silicone gel-filled breast implants, which we also will refer to as SGBIs, after market approval.

Additionally, this meeting is to provide transparency and a public forum for discussion of the postapproval study SGBI data and to provide an opportunity for stakeholder input and perspectives.

We have set a few goals for this Panel meeting. First, we are seeking recommendations from the Panel on approaches to design and implementation of postapproval studies for new SGBI submission applications. Secondly, we will be seeking recommendations regarding

surveillance in the ongoing SGBI postapproval studies.

We hope that through this discussion we will identify approaches that will maximize the feasibility and successful completion of mandated postmarket studies and gain input on innovative approaches to new studies. Additionally, we look forward to input from the public and other interested parties during these two days.

In 1991, a final rule calling for submission of PMAs for SGBIs occurred, and an Advisory Panel meeting to discuss these PMAs occurred also.

In 1992, there was a voluntary moratorium on SGBI breast implants, and FDA held a second panel meeting. At that time there was an adjunct study protocol for SGBIs for reconstruction and revision patients only.

In 1999, the IOM issued a report stating that there was no evident risks of connective tissue diseases for SGBI.

And in 2002, Allergan submitted a PMA for its SGBI.

In 2003, the FDA held an Advisory Panel to review Allergan's PMA, and Mentor submitted their PMA for SGBI as well.

In 2005, FDA held an additional Advisory Panel meeting to review Mentor's PMA and Allergan's updated PMA.

And in 2006, FDA approved both PMAs with conditions to conduct six postapproval studies that I will discuss in the following presentation. FDA also made a commitment to update the panel in five years

on the progress of the postapproval studies, and this is part of why we are meeting today.

In January of this year, FDA issued a safety communication on a slightly higher than expected rate of anaplastic large cell lymphoma in women who have silicone gel-filled breast implants. This is not the topic for today's Panel meeting, nor should it be considered as a potential focus of future postapproval studies as the FDA has just entered into a cooperative research and development agreement with the American Society of Plastic Surgeons to develop a registry specifically to actively monitor this very rare disease in women who receive SGBI.

In addition, in June of this year, FDA issued an update of the safety of SGBIs, including a newly designed website that includes extensive information for potential patients, women who already have implants, clinicians, and the public.

The highlights of the findings of the postapproval studies are included, following this presentation, as part of the update that FDA promised five years ago.

We would like again to thank the Panel members for their taking the time out of their schedules to help FDA on these issues, as well as members of industry, professional societies, patients, and the general public for coming and presenting their views on this issue.

I will now discuss the postapproval update for SGBI. Thank you

for your continued attention.

I would like to acknowledge the hard work of a number of my branch members who are here today and sitting over there and assisted with the preparation for this presentation.

I will first provide background information about the postapproval studies' condition of approval and key summary findings about postapproval studies, then give a short overview of each of the six postapproval studies. The primary focus of this update is to provide you information on clinical postapproval studies for silicone gel-filled breast implants.

Information about the Allergan and Mentor studies for each condition of approval are presented side by side for ease of presentation. Please note that none of the postapproval studies were designed to make direct comparisons because they differ in study designs.

I will close with preliminary study findings, conclusions, and future considerations for improving the current clinical silicone gel-filled implant postapproval studies, and then findings from adverse event reporting and current literature, as discussed in the FDA safety update, which is included in your Panel package and also posted on the web.

The silicone gel-filled breast implants were approved with six conditions of approval that are listed up here. There are two types of postapproval studies: nonclinical studies and clinical studies. The clinical

studies are highlighted in blue.

The approval letters required closure of enrollment of the adjunct study, the final study on that list, and continued follow-up of all adjunct study patients enrolled at the time of approval through their five-year evaluation post-implant.

The primary focus of this discussion is to update you on the clinical studies. And please note that at the time of approval, FDA provided both Allergan and Mentor with postapproval study questions, and each company was allowed to develop study design they believed would address the postmarket questions. Therefore, the studies differ, as I will discuss later, and reporting also differs, meaning that information you will see may vary from company to company.

Later during the deliberations, the Panel will be asked to consider if a standard reporting format across studies would enhance the ability for comparisons.

Long-term findings from the core study indicate that SGBIs continue to be safe and effective when used as intended. There are significant risks of local complications and adverse events. The complications that existed for women receiving breast implants at the time of approval are similar to complications observed at the 8 and 10 years of follow-up, except for the new finding of anaplastic large cell lymphoma, or ALCL. That, as noted earlier, is not part of the focus of this Panel meeting.

Breast implants are not lifetime devices. One in five women who receive implants for augmentation and one in two women who receive them for reconstruction will require removal 10 years after implantation.

The benefits and risks of SGBI are sufficiently well understood for women to make informed decisions about their use, and most women are generally satisfied with their choice.

Now, I will begin with a description of the nonclinical studies in the next slide and then follow with a discussion of the clinical studies.

The nonclinical postapproval studies are listed here. The focus group study was designed to improve the format and content of patient labeling. Each manufacturer held focus groups and modified their brochures and/or product labeling based upon the findings of these studies. These studies are now closed.

The device failure studies and informed decision postapproval studies are ongoing and will continue with all subjects in the large postapproval studies, until the large postapproval studies have completed their 10-year follow-up or reached the end of the window for the 10-year follow-up.

The device failure studies are designed to further characterize the modes and causes of failure of explanted devices that are retrieved and returned over the 10-year period.

The annual informed decision survey is a random sample of 50

physicians each year and is designed to monitor the progress of how patient labeling is distributed to women considering SGBI.

I will now provide an overview of clinical studies.

Participants in both of the core and large studies that I'm going to talk about were enrolled into one of the following surgical indication cohorts: Primary augmentation cohort consisted of women who received breast implants to increase the size of their breasts. The revision augmentation cohort consisted of women who received breast implants to correct or improve the results of primary breast augmentation surgeries.

The primary reconstruction cohort consisted of women who received breast implants to replace breast tissue that was removed due to disease or trauma or that failed to develop properly. The revision reconstruction cohort consists of women who received breast implants to correct or improve the results of primary breast reconstruction surgeries.

For each clinical study I discuss, the results presented will appear in this order that you see here.

This table shows the follow-up goals for both clinical studies I'm about to present. Both companies agree to the same range of year-specific target follow-up rates that would ensure a target of 65 percent follow-up rate at 10 years.

First let's turn our attention to the objectives, study design, and preliminary results of the core studies.

This table summarizes the design of the core studies. The purpose of the core studies was to gather data on longer-term safety and effectiveness of SGBI implants among participants enrolled in the studies conducted to support premarket approval applications. These studies did not include a comparison group and are to follow women for up to 10 years after they receive the implant.

The Allergan core study enrolled 715 patients and the Mentor core study enrolled 1,008 patients. Data were collected at baseline and during the follow-up clinic visits. Follow-up clinic visits included a physical exam and an assessment of adverse events and a self-administered patient questionnaire.

Allergan follow-up rates at 10 years post-implant are 66 percent. Mentor follow-up rates at 8 years post-implant are 58 percent. Longer-term follow-up is available for the Allergan core study participants because the study began enrolling patients approximately 20 months before the Mentor core study.

Prior to device approval, each study assigned patients to either an MRI group or a non-MRI group. Participants in the MRI group received MRIs on a specific schedule to screen for rupture, as well as an MRI if a rupture was suspected at another time.

Women assigned to the non-MRI cohort had MRIs to detect ruptures only if a rupture was suspected based on symptoms or the

appearance of the breast.

The timing of the MRI assessments and the method of assigning participants to the MRI group differed by manufacturer. Following device approval, all women received MRIs based on the schedule set forth in the labeling.

It is important to note that these studies are not designed to estimate the incidence of rare adverse events, there is no comparison group, and the loss to follow-up can introduce participation bias.

The next several slides present the core study results for Allergan at 10 years post-implant. Similar results from Mentor at eight years post-implant will follow.

The enrollment numbers for Allergan are shown here by indication cohort. A larger number of patients received implants for primary augmentation. Note that in the Allergan study the revision reconstruction group is very small compared to the other indication cohorts. As a consequence, the results for this group are difficult to interpret.

Most women report being generally satisfied with their implants, including the shape, feel, and size of their breast as well as their perception of their body image. Additionally, most physicians reported that they were also satisfied with the outcome.

The complications that existed for women receiving SGBI at the time of approval are similar to the most frequent complications observed at

10 years. The proportion of women experiencing local complications varied across indication cohorts, with those receiving implants for primary augmentation being lower compared to those receiving implants for primary reconstruction. The incidence is highest for reoperation.

Although not shown here, preliminary data do not indicate that SGBI caused breast cancer, reproductive problems, or connective tissue disease up to 10 years. However, the core studies were not designed to detect these associations.

I will now present data for the eight-year data for Mentor core study.

The numbers for enrollment in the Mentor core study are shown here. As with the Allergan study, a larger number received implants for primary augmentation.

Similar to the Allergan study, most women report being generally satisfied with their implants, including increasing size of their breasts as well as their perceptions of body image, feelings of well-being and self-esteem.

As with the Allergan core study, the complications that existed for women receiving SGBI at the time of approval are similar to the most frequent complications observed at eight years. Again, the proportion of women was lower in the primary augmentation cohort compared to those in the primary reconstruction cohort.

And as with the Allergan study, the preliminary data do not indicate that SGBI caused breast cancer, reproductive problems, or connective tissue diseases up to eight years. And I caution again, the core studies were not designed to detect these associations.

So just to reinforce again some cautions about these studies, due to differences in the study designs, comparison across studies is not appropriate. Secondly, the core studies were not designed for the incidence of those rare diseases I was discussing. Nor were they designed to compare silicone gel-filled breast implants to other types of breast implants or other alternatives. Finally, the low follow-up rates do limit the interpretation of the findings.

I will now turn my discussion to the large postapproval studies. And just to state, because I didn't, both of these studies are still ongoing and this is preliminary data.

The large postapproval studies are designed to gather additional information on rare adverse events and events that occur after a long period of follow-up. Studies are powered to detect the rare events. The large studies were both designed as multicenter, prospective studies with 10-year follow-up from the data of implantation surgery. Both studies used saline controls as comparators for all endpoints.

National norms were also used as control for the rare endpoints, including the connective tissue diseases, the rheumatologic signs

and symptoms, neurologic diseases, neurological signs and symptoms, cancers, suicide, reproductive complications, lactation complications, and offspring complications.

Each sponsor was required to enroll approximately 40,000 women receiving SGBIs and follow them for 10 years. Enrollment is closed for both studies. Saline implant recipients were enrolled as concurrent comparison groups.

Each company developed a different study design. For example, in the Allergan study, the control group was selected from all women. For the Mentor study, the control group was selected as a 10-percent sample of the first 10,000 women. In addition, the windows around follow-up visits varied between the two studies.

The follow-up rates for both large studies for the silicone cohort are shown here. FDA will present findings of the saline comparison groups at a later date.

The highlighted row, which is the pink row, shows the follow-up goals to which both companies agreed before the studies started. This is based upon the table that I showed you earlier. Note that all the rates are below the targets of 93 percent for 2 years and 89.5 percent for 3 years. The denominator used to calculate follow-up rates includes only subjects who have passed the end of the time window for that follow-up.

During the questions, the Panel will be asked to consider

strategies for improving follow-up rates in postapproval studies. Additionally, at the end of this discussion, I will present some -- later this afternoon I will present some of the things that FDA did to try and improve the follow-up rates.

Now I will discuss the Allergan large postapproval study at two years post-implant.

The patient enrollment for the Allergan large study is summarized here. The table shows the number of participants in each indication cohort and the percentage that each cohort contributes to the total number of participants for the study.

Allergan is still in the process of examining and reporting the number of augmentation patients younger than 22 years of age who were included in the study. The current number of augmentation patients in the table include at least 97 women who were younger than the qualifying age for this study, which was 22 years old for the primary augmentation cohort.

Allergan reported the estimated two-year cumulative incidence of local complications for the overall cohort of women and not by indication for the implant. The most commonly reported outcome was reoperation, followed by capsular contracture.

I will now discuss findings for Mentor's large study, which includes data at three years.

The patient enrollment for the Mentor large study is

summarized here. The table shows the number of participants in each indication cohort and the percentage that each cohort contributes to the total.

This slide shows the three-year cumulative incidence rates for Mentor for local complications by indication cohort. Similar to complications for Allergan, the most common complication was reoperation. Rates do appear higher in the reconstruction cohorts, and the primary reason for reoperations were size change at the patient's request, infection, and asymmetry.

The adjunct study is the sixth and final study I'm going to discuss. The objective of the study was to provide information about silicone gel breast implants provided to women in the U.S. from 1992 to 2006, when implants could only be used for reconstruction and replacement of existing implants. The status is ongoing, and all women are being followed for five years after their initial implantation.

Enrollment of patients was close for both studies at the time of approval. Follow-up of the adjunct study subjects will continue until all women exceed the window for the five-year follow-up. Currently, the follow-up rates are presented here and are far below the 80 percent expected at five years.

So just a few key points for the current postapproval studies. There were six postapproval studies as a condition of approval. Three were

nonclinical, and one was a study of the women receiving reconstruction surgery prior to the current device approvals, and two were clinical studies ordered after approval. Observing longer-term data for local complications, we see that the pattern that we did see at the time of approval is still the same.

We conclude that breast implants are not lifetime devices. However, routine replacements are not necessary. The longer a woman has SGBI, the more likely she is to experience a complication at 10 years, and we know, for the primary augmentation patients, one in five will require an implant removal, and among primary reconstruction patients, one in two will require removal.

Based upon data in the postapproval studies to date, there appears to be no apparent associations between SGBI and connective tissue diseases, breast cancer, or reproductive problems. However, due to the limitations of the follow-up data, these associations may not be detected.

Direct comparisons between the two studies are not appropriate due to differences in study design, clinical endpoints, and patient populations. Low follow-up rates limit the ability to draw definitive conclusions. However, later this afternoon, as I stated before, I will also present actions that FDA had taken with the companies to increase follow-up. And to stress, these are interim findings of currently available data, and data collection for both studies is still ongoing.

Now I'm going to turn to talk more about postmarket surveillance of adverse events outside postapproval studies.

FDA collects and analyzes adverse event information from a variety of sources. Manufacturers and user facilities are required to report events through the Medical Device Reporting system, or MDR. Patients and health providers may also report adverse events directly to the website noted on this slide. Searching the term MedWatch will also identify this site. We encourage both patients and providers to report adverse events and other concerns to the MedWatch system.

In addition to MDR reporting, usual complications and malfunctions for SGBI are reported quarterly through the postmarket spreadsheet reporting requirement. These are sent separately from the MDR reports, which are specifically for unusual and unexpected events.

There were 133 MDRs for SGBI from device approval through 2010: 24 were from manufacturers, 25 from user facilities, and 84 were voluntary. There were two reports of ALCL, both from the same patient. And this is overall consistent with what would be expected based on numbers.

Since reporting is voluntary for patients and providers, the number of events is often much lower than the number of events that actually may occur, and the reports may contain inaccurate or incomplete information that FDA cannot independently verify. The size of the population or the denominator is also not known, so it is difficult to determine the rate

or associated causes and interpret the data.

In January of this year, FDA released preliminary findings and analyses regarding reports in the scientific community about a possible association between anaplastic large cell lymphoma (ALCL) and breast implants. The incidence of ALCL is extremely rare. However, FDA believes that women may have a small but increased risk of developing this disease in a scar capsule adjacent to the implant. Based upon available information, it is not possible to confirm with statistical certainty that breast implants cause ALCL.

As noted in my introductory remarks, since this collaboration will be addressed with the registry that we have set up or will be setting up, it is not the focus of our postapproval discussions this afternoon or tomorrow.

FDA conducted a review of the medical and scientific literature as well, from January 2005 through December 2010, and found that most women are satisfied with the outcomes of their implant surgery. It was noted that infections following SGBI implantations mostly occur in the immediate postoperative period. With the caveat that establishment of a causal relationship between SGBI and CTDs would require a large study of sufficient duration due to the incidence and prevalence of these diseases, most studies have not found an association between CTD and SGBI.

One study did find an association, but it had significant study design and patient selection weaknesses that undermined the study's

conclusions. Overall, the current body of evidence does not support this association.

There was no evidence of associations with cancer, except for the rare development of ALCL that I just discussed. There was no evidence of associations with reproductive or lactation complications or suicide risk.

This concludes my presentation for this morning. Thank you.

DR. LoCICERO: I'd like to thank Dr. Krulewitch and the FDA representatives for their thorough presentation.

Does anyone on the Panel have any brief clarifying questions for the FDA? And remember, all of the Panel will have opportunities to ask further questions of the FDA later today and tomorrow.

Yes, Dr. Glassman.

DR. GLASSMAN: Leonard Glassman.

I'm a little concerned about the fact that reoperation is such a broad category, and it's very difficult to get a handle for me on why people were reoperated. Was it surgeon failure? Was it patient expectation failure? Was it device failure? Is that data available, although not specifically reported?

DR. KRULEWITCH: Some of that data is available, although not reported, and some of that will also be something, I think, that would be a very fruitful discussion for this afternoon, as to what we need to collect in the future.

DR. LoCICERO: Dr. Connor.

DR. CONNOR: Jason Connor.

I have a few brief questions about the core study. Are all of the women in the core studies out to 10 years, for instance, in Allergan or eight years in Mentor?

DR. KRULEWITCH: No.

DR. CONNOR: Okay. So then I think my question is, the rates we saw for follow-up, are they just the proportion of those who could be out to 10 years who were still tracked? Are they Kaplan-Meier estimates of people who made it to 10 years? How were those follow-up figures arrived at?

DR. KRULEWITCH: Those are all based on those who made it to the window.

DR. CONNOR: Okay.

DR. KRULEWITCH: So they can change.

DR. CONNOR: Okay. So can you tell us how many there are, then, since not everyone in the core study is out that far?

DR. KRULEWITCH: I can get that for you.

DR. CONNOR: Okay.

DR. LoCICERO: Any other questions?

DR. CONNOR: Can I ask one more?

DR. LoCICERO: One more.

DR. CONNOR: So something that you mentioned, and I read a lot in the pack, was that the longer a woman has her implants, the higher the complication rate goes. And so by definition that's true. The longer you have anything, the rate can only go up; it can't go down. But I wanted to confirm that you weren't implying that the actual hazard was increasing over time because I don't think that's true. And, in fact, is that going down dramatically?

I mean, we see that infection sort of peaks right after. Is it true, then, that if we plotted the hazard, that it's actually pretty low after a particular window?

And I think seeing Kaplan-Meier curves for a lot of these different things would be helpful to both us and even to doctors explaining things to their patients, to say, you know, some of these events, if you don't have them in a certain window, it's probably okay then, or your risk is much less after that. So I think for both, you know, FDA and the companies, showing Kaplan-Meier curves for some of these things would be very helpful.

DR. KRULEWITCH: We can present some of those later, if the Panel wishes to see those. The rates were not -- I can tell you that, for at least the main, the rates were not increasing. They were probably remaining steady. But yes, because it's a cumulative incidence, more women are seeing the problem.

DR. CONNOR: Okay, thank you.

DR. LoCICERO: Other questions? Just for clarification, a lot of cancer studies that are performed have expected accrual rates, and this is slightly different. Has the FDA worked with the sponsors to establish expected percentage follow-up? And if so, have those been met?

DR. KRULEWITCH: The table that I presented earlier were the expected follow-ups, which is in your packet there. And no, they have not met the follow-up. And this afternoon, right before we go into questions, I'll talk a little bit about the actions that FDA took with the sponsors and worked with the sponsors, and I imagine that they're also going to discuss that in their presentations, as to the things they did to try and increase the follow-up rate.

DR. LoCICERO: Any other questions?

(No response.)

DR. LoCICERO: Well, we're running slightly early. Thank you very much. Let's go ahead and take a break now before we have the sponsor presentations. Hopefully we can continue to run ahead of time. Let's be back in 10 minutes, please.

(Off the record.)

(On the record.)

DR. LoCICERO: It's now 9:23, and I would like to call this meeting back to order.

We have two 30-minute sponsor presentations scheduled for

Allergan and Mentor, which will be followed by a brief question and answer period by the Panel. Allergan will be first and will now give a 30-minute presentation.

DR. AVELAR: Good morning. Thank you for this opportunity to present, Panel and Chair.

First, I'd like to set the expectation and go through the objectives that I have and what I hope to cover in the next short while.

When the FDA called this meeting and made us aware of this Panel presentation on the topic of postapproval studies, we were asked if we could come and share our experience with postapproval studies and what we've learned during the course of the challenges we had and what we did to try and overcome some of them. And in the end I'd like to try and make some comments that may be of help as the Panel considers postapproval studies.

A quick historical slide. This has been covered. But 1999 was when the core study began. It took about a year to enroll that. In 2000, it was completely enrolled. In 2005, of course, there was a meeting, and then, 2006, the ultimate approval.

The core study was then converted into a postapproval study in 2007. One of the conditions of the approval was that we would do a large postapproval study, the BIF study, which was outlined just awhile ago. And subsequent to that, one of the conditions of approval was that industry would continue to update physicians, patients, the FDA with data. And in

2009, the label was updated and seven-year data was provided.

And just a quick update that I don't think the FDA is aware of. But just recently, as in a few days ago, we did complete our 10-year data for the core study, and we have submitted it to the FDA, so that should be arriving any day now. So the 10-year data from the core study will now be available. We're not here to discuss that, but hopefully that'll be of help for everybody.

In 2005, there were a number of questions and there were discussions with regards to local complications. Rupture rate was a topic of interest, as was reproductive implications of breast implants. And there were a number of questions regarding systemic implications. Was there an association with silicone breast implants and cancer or connective tissue disorders or not? There was a great deal of data that had been generated prior to that, suggesting that there wasn't. However, we don't know and that's why we do studies.

The FDA, in 2006, November 2006, ultimately approved the Allergan silicone breast implant, and there were six conditions of the approval. I'm going to highlight the first two. But the core study, which was originally a pivotal study, was then converted into a postapproval study, and the understanding is that we'd follow it for 10 years.

The large BIF study, of course, was instigated, and there was an understanding that we would look at device failures, and to date, we've

actually looked at over 3,500 devices that have been returned to us. We try to analyze what happens to them in the real world as we get them back. Why do they rupture?

And just a quick sidebar. Sixty-two percent of those implants that arrive are actually not ruptured. But we've been able to learn -- we're trying to learn more about the failure modes of those products.

We committed to doing some focus group studies, trying to understand the material that we put out for patients, the labeling that we give to patients. Is it accurate? Is it representative of the data that we have on the performance of the device? And we also look annually at physician interactions with patients to understand, is the disclosure process -- is the informed consent process appropriate? And then finally we committed to completing the adjunct study, which is at 84,000 patients right now.

The core study, as mentioned already, is a 10-year observational study, and it looked at two things primarily, effectiveness and safety. On the safety side, we looked at local complications, and we tried to understand why implants were removed. Why do people undergo reoperations? And we tried also to look at the systemic implications of the silicone implants, although we all acknowledge that this trial really wasn't designed to do that.

Effectiveness. At the end of the day, these are patients who undergo these operations, and one of the important elements to consider is

the patient. Are they satisfied? Ten years later we may look at these Kaplan-Meier curves, but what is their satisfaction level at 10 years? What is their quality of life?

With respect to the design of the study, there are a couple of things that are of note and of interest. First of all, when we look at the complication rate and reoperation rate, it's important to note that we have office visits that are at from zero to four weeks. So when we look at overall events in these studies, we actually capture a lot of the perioperative phenomena like breast swelling, breast pain -- naturally underwent a surgical procedure. A number of them will actually have a lot of these complaints and a lot of these complications, perioperatively, within the first month. We also look at the six-month interval, and then we follow these patients annually for 10 years post-implantation.

Within the trial there was an MRI subset, and initially, during the core study, the subset underwent MRI examination at year one, three, and five. And then after the study was converted into a postapproval study, all of the patients underwent MRI. So in the seven-year and nine-year time interval, every patient had an MRI.

This is what the enrollment looked like. You see a large representation of primary augmentation and then revision aug and primary reconstruction and a much smaller representation in the revision reconstruction group.

The MRI cohort was 264. Largely representative there was the primary augmentation population and equal representation in the primary reconstruction and the revision augmentation.

So what have we learned? Well, 10 years later, what we've actually learned is a lot. What we've learned was that, in 2005 when -- in 2006 when the approval was made, what we learned was we didn't really see anything new. The things that we expected, the things that we saw in 2005 continued in 2006, 2007, 2008, and the 10-year results now, I think, are fairly consistent with what we expected back in 2005-2006.

I did take the liberty of adding just a couple things here. If you look at capsular contracture, that's the kind of complication that you'd expect over time to increase. And things that sometimes confuse people -- and the question was asked about the Kaplan-Meier. A number of the complications here actually occur early. So although you may see a 10-year title and you see things like breast pain and swelling and implant malposition or nipple complications, these events are quite frequent, but they tend to take place more often early on and they're captured in that zero-to-four-week window that I had mentioned early on. Hence the larger representation.

There were a number of systemic implications that people want to look at, and consistent with what the FDA said earlier, we've not been able to see -- we have not been able to identify a connection between silicone implantation and things such as connective tissue disorders or breast cancers

or suicide.

I've put here, to be granular, the incidences or the actual events that have taken place. You can see in augmentation two rheumatoid arthritis patients, two fibromyalgia, and one Reynolds syndrome. And we all acknowledge that this study was not designed to try and bring an answer to this, and we all acknowledge that there were limitations in the study, in the context of systemic implications. But, again, this seems to be fairly consistent with what we've seen, and we have not seen a connection.

At the end of the day, again, these are patients and we may obsess over the numbers and the complication rates, but when we actually take a step back and ask the patient how they feel 10 years later, and we look at things like patient satisfaction and quality of life, the results are very high. If we look at the revision augmentation population, over 80 percent of patients are very satisfied with the result. And if you look at the primary augmentation, satisfaction rate is in excess of 90 percent. And the same holds true for the reconstruction patients. Again, if we look at the revision reconstruction patients, satisfaction rates in the high 80s, and in the primary construction patients, these patient satisfaction scores are in excess of 90 percent.

The large BIFS follow-up study. Just quickly, this is a 10-year observational study; and females over the age of 18, and for breast augmentation, over the age of 22. And what is consisted of was primarily

annual questionnaires for all subjects. And there were physical examinations, and they took place at three time intervals, year 1, 4, and 10.

And the objective of the study was to have a much larger database, a much larger number, and to try and understand the long-term safety implications, connective tissue disorders, and the other events of interest that we'd identified, and to see if we can understand pregnancy outcomes and lactation. Certainly, we haven't seen a connection to date. We all recognize the limitations of the studies that have come out to date and some of the questions within those studies. But this is another dataset trying to bolster up the data that exists today.

I do want to point out that you'll notice there's an MRI component here, but it's not MRI results. We're not looking at sensitivity or specificity of MRIs in this case, but rather what we're trying to understand is, once these trials go into the real world, are patients compliant or not? So, effectively, we're trying to understand what is the compliance with the actual MRI recommendations.

Enrollment. The first patient was enrolled in February of 2007. And I'd like to point out that it took almost three years to enroll these studies. When we do these studies and we think about postapproval studies, we may start at time zero and we may have the best intent when we design the studies, but I think it's important to understand, preemptively, that it can take a long time and the world can change during the course of a study, and

when we think about these designs, how much flexibility is within the design?

I also want to point out another thing. One of the premeditated decisions that was made was patients were given the option to enroll in the study or not, and the thought behind that was, if patients willingly acknowledge that they wanted to be part of the study, perhaps that would help with the compliance, as opposed to mandating their participation. The repercussions of that was it took three years to enroll the study.

The breakout: we have 41,000 silicone patients and about 15,000 saline. The comparator here is saline and normal population. And there were a lot of sites involved, over 1,000 sites, which has implications in terms of coordination.

When we look at the two-year and three-year data, obviously we're very early on. We can see that we're talking about 12,000 patients in year two and close to 3,000 patients in year three, simply because the study is just ongoing right now. We see numbers that are fairly consistent with what we've seen in all the other studies. We see a capsular contracture rate in about five percent. We see implant ruptures as complication risks. And we also look at other things like reoperations, implant removal, and replacement.

Again, just to add a little bit of clarity, when we look at reoperations, one of the questions that was asked was, what does it mean? And in our latest 10-year report that we just submitted, it's broken down. It's relatively easy for us to break it down, and we'd be happy to submit that to

the Panel.

But a lot of these reoperations actually consist of things like needle biopsy. So anything that allows -- that necessitates a reoperation, not necessarily pertaining to the breast implant, gets counted. Capsular contracture is probably the number one reason for reoperation rates both in the augmentation and the recon. But if we look at the augmentation, 50 percent of the implant removals were because of a request for a size change.

Patient's perspective. When we look at postapproval studies, we can design them, we can have a device, but the patient needs to be involved. And when we were trying to see what we could do to improve our compliance, we spent a lot of time and a lot of effort talking to patients, and we initiated focus group meetings and we asked patients, why do you participate? Why do you come to these things? Why do you elect to help us out with these postapproval studies? And the answer is really simple. Some patients like the compensation. That's an issue for all of us because we have to be careful about how we incentivize patients, because we can create conflicts of interest and there are laws that prohibit that.

Another reason why patients enjoy or want to be part of it is, if it's fast, if it's easy, they're happy to help out if the questionnaires are simple, and a lot of patients have a strong interest in the subject matter, so they'd like to be part of that.

We also ask them why they don't participate, and one of the

number of reasons why they don't, which has implications for the study design, is the questionnaire is overly burdensome. We're trying to extract too much information. It's a diminishing return for them. The more information we want -- and as scientists, as physicians, we may want this information, but it acts as a deterrent quite often to the patient.

And some of it is just simple misunderstanding. Some patients believe that MRIs actually have ionizing radiation. They don't understand the concept of it.

A lot of patients are just simply healthy. They participate for a little while, they're fine, they're happy, they move, they get married, they move to different cities. They're just healthy.

And some of them have concerns about confidentiality. A lot of patients who have undergone these procedures, the changes are subtle, and they don't necessarily want people to know that they had a breast augmentation or they had a reconstruction or that they had hypoplastic breasts.

And then finally, you know, industry may be trying to be very aggressive in trying to bolster up the compliance, but a lot of these patients are quite skeptical and they're skeptical about the sponsor's motivation. Why does this company want this information from us?

If we take it one step further and ask, what about the -- is there anything different about the reconstruction patients? The answer is they're

different from the augmentation patients. They tend to be more focused on health and safety. They've undergone a very traumatic event and it quite often is life changing. They're less motivated by compensation, as compared to the augmentation, and there's a very, very strong connection to trying to help other women.

Why don't they participate? Really simple. A lot of these patients simply want to forget what they went through. They do not want to be reminded about the fact that they had cancer, the chemotherapy and the procedures that they went through.

Just to kind of highlight the differences between these two cohorts -- and again, when we consider postapproval studies and we think about designs and we try to set expectations for follow-up, for instance, we could see right here, so far, in our BIF study, the silicone augmentation patients come in at about the mid-60s in terms of compliance, and you can see the silicone reconstruction patients, all in excess of 80 percent.

In the talk earlier, there was mention of the 22-year-old cohort or patients in the augmentation of less than 22. We had 97 of those patients in our trial. Their compliance rate here is about mid-20s in terms of percentage.

Lessons learned from focus groups. What else did we learn? Well, most patients acknowledge that if they have a reminder, that helps them. You know, if you can remind me I'm part of these trials, that would be

great. And so there was a lot of time and effort again spent on e-mail and mailings and telephone outreach programs to facilitate to remind them.

And we also took into consideration preferred methods of contact. Some patients do not want to be called. They prefer e-mail because they don't want their boyfriends to know what's going on. And so we try to personalize that for each person.

The website, the web is an integral part of all our lives right now. We try to facilitate that by making online questionnaires, making it simple.

And we did a whole new direct mailing that was actually much more directed to patients and stood out a little bit more from other pieces of items that could show up in the mail.

Call centers. We increased the personnel and we increased the hours. These patients have jobs, they have lives that they live through, so we try to facilitate that.

We created a symbol and, you know, if you step back and talk to these people, there's an appeal, and the appeal is to the common motivator among these subjects to help other women and yet at the same time have their own voice heard. So when we looked at the BIFS symbol, it symbolized to them the power of one and the strength of many.

We were able to take the symbol to do simple things. So for instance, we all get a lot of mail. What's junk mail and what's actually

legitimate? So by simply putting this BIFS logo on, patients can readily distinguish between a reminder piece of mail that is actually relevant and something that isn't.

And again streamlining the website, we did little things like interactive e-mails, personalized them so that they uniquely are a unique tribute to each one, and we made it simple by adding menus that spoke to appointments and questionnaires.

And then finally, trying to capture data, there are a number of us who are experts in terms of running trials and understand CRFs and electronic data captures, but patients, it's a little bit trickier. So if you send them a simple e-mail reminder and with the click of a button you can log on to complete your questionnaire, it makes everybody's life easier and helps with our compliance.

You've seen the compliance number overall, and I thought I'd just add, this is new information. If we look at the silicone compliance cohort year one, year two, year three, right now we're tracking at about 67 percent. And we were able to capture a lot of the patients, the first year patients who didn't show up for their first year questionnaire, and catch them later.

To give an order of where we are in terms of update, again, if you remember when the trial's fully enrolled, our first year compliance number really won't be confirmed until November of this year. That's when all the first year patients will be in. And, of course, there's the window for

year two and year three, and we're only starting right now to capture the year three.

Thoughts on postapproval studies. Well, hindsight's always 20/20, and when we look back at what was happening in 2005 and 2006 and we looked at the concept of the core study and the BIF study, there were a number of questions. People wanted to understand things more.

And we may talk about case control studies and how to pick up these rarer events, but at that time we didn't know, and if we do a cohort design, we can go for it, we can anticipate the things that we want to study. But with the open frame and the lack of biases, we can actually pick up events that we never imagined, that we never thought of. That's why these CRFs have things like unexpected events, so we can capture this. And so having gone through this experience, it was probably the right choice, and we probably did the right study.

I think, at the same time, it's really important to acknowledge that even a large study like BIFS will never pick up the very rare events. It just won't. It's not designed to. And the ALCL is one of those examples of an event that just wouldn't be picked up by that.

And as much as we can talk about how to run these studies, how to understand these products in the market, I think we have to acknowledge there are other mechanisms there, and perhaps we can leverage them a little bit more effectively in helping us understand

performance. We could look at postmarket surveillance. We have the MDRs, we have the alternative summary reporting, and we have the postmarketing spreadsheet reporting.

Companies take a lot of time to do annual reports and review the literature. And at Allergan, we actually have a safety panel now, where we try to look at our products and try to scrutinize the data that exists and try to pick up signals and try to pick up trends. And we're very grateful for the physicians in this world and the patients in this world who actually stand up and file MDRs and make us aware of the issues so that we can actually be proactive.

And hence, at the end, when we start to identify these signals, when we start to recognize that perhaps we've looked at something, perhaps that's the best time to start talking about case control designs, where we can be much more efficient at looking at those rare events.

I do want to make one comment, and particularly from an industry perspective. When you create a product, I mean, the ambition is always to create something and try to improve with our lessons learned. So innovation is a really big deal because it impacts us all. It allows us to come up with better and new products.

And so when you're introducing a new product, probably that cohort design is the right design because it's new and we don't know about it and we can go forward. But if we're trying to introduce a product

modification, if we're trying to introduce something that's a version of something in that study, it would be very helpful if we actually leverage the body of knowledge that has already been established.

And if we can design studies, of postapproval studies, that actually try to hone in on the differences between what is the new element of this product versus what has already been established, that allows for a more efficient design, a more efficient process, and it also allows us to build on the established knowledge base that we've put together.

So my last slide. Why do we do postapproval studies? Well, we know why we do that. We're trying to address questions from the pivotal studies, and we're trying to assess the effectiveness and safety of all of these products as they go through the real world and their product cycle.

But the one thing that I think is important for us all to kind of ground ourselves with, at the end of the day, as we go through these designs, I think it's important to sit back and reflect and think, are they clinically sound? Are these designs realistic? Are they executable? Because, at the end of the day, once they're out there, somebody has to execute on these trials. And, finally, most importantly, does it benefit our patients? Thank you.

DR. LoCICERO: Thank you. Mentor will now give their 30-minute presentation.

DR. CANADY: Good morning. On behalf of Mentor Worldwide

and its 1200 employees, I would like to thank the Food and Drug Administration for inviting us to today's Panel hearing.

I'm Dr. John Canady, Mentor's medical director, and today we will present recommendations for how future postmarket surveillance studies could be designed to include a variety of data sources, many of them already in place, about the safety of silicone breast implants.

I think it would be fair to say that we are all here today because we care deeply about patient safety. I joined Mentor in March, and one of the many reasons for this move from academia was that we shared this passion. In fact, Mentor's top priority has been and always will be patient safety. But such a priority demands a commitment and a focus, and for Mentor this commitment was to ongoing research.

Since it was founded more than 40 years ago, Mentor has remained committed to investing in research aimed at future enhancements and advancements of the products and procedures surgeons use to restore body and life for patients.

My first concern when I was in clinical practice at the University of Iowa was the safety of my patients. My first concern now that I'm medical director is still the safety of the patients who use our products.

I'm glad that the data continues to support the safety and efficacy of breast implants. The current large postapproval study unfortunately, though, has not given us the additional data we hope for. But

I can assure you that plastic surgeons have tried hard in this effort. I saw that when I was president of the American Society of Plastic Surgeons, and I know that manufacturers have also tried hard. I see that now as medical director.

The constant finding through all of this seems to be that patients who feel well just don't go to the doctor or fill out medical paperwork. I saw that to be true in my own practice in plastic surgery, and even as a child growing up, I don't remember people who felt well sitting in the waiting room of my dad's family practice clinic.

We at Mentor are committed to continue to pursue good, sound safety information for our medical devices. But we think there's a better way to do that. Today we will briefly review where we've been, where we are now, and then respectfully suggest some ideas to approve the approaches going forward.

At this point I would like to introduce Dr. Roger Wixtrom, a board-certified toxicologist who has been intimately involved with the science of breast implants for more than 20 years. Roger will share with you how ongoing core studies, reviews of the public literature, expert panel reviews, and enhanced postmarket surveillance could be utilized to address previously stated objectives for PAS. When Roger is finished with his presentation, I will be back to make a few closing comments. Thank you.

Roger.

DR. WIXTROM: Thank you, John.

To frame today's presentation, the objective that FDA set forth for postapproval studies was to help ensure the continued safety and effectiveness of the approved device, and Mentor is certainly fully committed to working with the FDA to ensure that that objective is met.

What I'd like to do in my portion of the presentation today is to share information with you beyond what was in your information packet, some information to hopefully inform the discussions to follow in the next two days.

Now, with respect to the postapproval clinical studies for the MemoryGel breast implants, the two that I'm going to focus on today are the MemoryGel core study, about 1,000 patients being followed out to 10 years, and the MemoryGel large postapproval study, with approximately 43,000 patients enrolled, also being followed out to 10 years.

Both of those are prospective, multicenter clinical trials. Both of them incorporate physician visits at various intervals, and the large PAS relies also on patient questionnaires on an annual basis. As you saw in this morning's presentation, these cover a very wide range of study endpoints, from local and perioperative complications to the more rare health endpoints. And annual updates are provided to FDA for both of these studies.

Now, what we've learned and the experience that's been gained from those studies is what we'd really like to spend some time sharing

with you this morning as we consider both the current situation and then also designing studies in the future.

With respect to what's been seen, as was mentioned earlier this morning, the most frequent complications and adverse outcomes experienced by breast implant patients in the core studies were capsular contracture, reoperation, and implant removal.

Now, if we look at the rates for those, in the left-hand column there, we see that, for capsular contracture, the cumulative incidence through eight years was approximately 11 percent, reoperation approximately 20 percent, and device removal 7.3 percent.

We thought it'd be interesting for the discussions today and tomorrow to look and see, we have interim findings for both of these studies at this point. For the postapproval study, we're at three years; for the core study, we're at eight years. But if we take a look at the three-year time point, for which we have data from both, for these most frequently experienced complications, what we see is, for both capsular contracture and device removal, a remarkable degree of agreement.

Now, with reoperation, what we've seen is a little bit lower reoperation rates, and the hope from those who have seen this data is that it may reflect a number of initiatives in plastic surgery to really bring down the reoperation rates for these patients. And, in fact, the studies have about a five to six-year difference in their start time.

Now, speaking a little bit more about reoperation, as was mentioned in the previous presentation, reoperation includes both procedures done that are device related and non-device related. And if we look at the primary augmentation cohort, the three leading reasons for reoperation, one was device related. That was capsular contracture, and that represented 30 percent of all reoperations seen in the first eight years. The second two were non-device related. Size change accounted for 14 percent of all reops and hypertrophic scarring for 11 percent.

Also, almost identical to the results you heard in Allergan's presentation, if we look at explantation for the primary augmentation cohort, 53 percent of those explantations were due to patient-requested size change.

Now, despite the significant rates of reoperation, as you saw in the previous dataset, the satisfaction rates among these patients remain very high and very similar between cohorts. Amongst the primary augmentation patients, 97.5 percent said that they would have the surgery again at the eight-year time point, whereas 97.4 percent, nearly an identical percentage of patients who had undergone reoperation, also reflected that feeling.

And I think for any medical device that's approved and one's looking at it in the postmarket setting, one of the things one really hopes to better understand is device failures and why do devices fail. And with these breast implants, that's an issue that's addressed with one of the conditions of approval, the device failure studies, and these studies examine devices that

are returned over time.

And for the Mentor device failure study, if we look at the full set of devices evaluated, which are not just those in the core study or large PAS but any of the devices returned in this time interval worldwide, there's more than 3,000 devices that have been evaluated.

Now, with the breast implants, Mentor offers a lifetime product warranty, and one of the conditions of that warranty is that the original device is to be returned to the manufacturer to qualify for the reimbursement, and that really helps in terms of ensuring a high return rate.

Now, in the modes and causes of failure studies on those returned devices, what we've seen is that the majority of failures, 63, 64 percent actually of the failed devices, it's due to sharp surgical instrument damage. And that's actually quite easy to detect if you're looking at one of these returned implants under the microscope.

If you look at that left image, that reflects what you'd see. That's very characteristic damage from a needle puncture. In the center image there's this striated pattern on a very smooth-edged surface. That's quite characteristic of surgical scalpel damage. And both of those are quite distinct from the right-hand image, which shows what's termed a fishbone-type pattern, which is very characteristic for fatigue wear.

Now, the information that's been learned from these device failure studies has now been turned back into professional education

materials, it's captured in device labeling, and there's new initiatives underway to help reduce these sharp surgical instrument damage failures over time.

Now, with respect to detecting breast implant rupture, as you heard in one of the earlier presentations this morning, MRI remains the most effective method for detecting rupture, and the current FDA recommendations are that screening begin at three years and then continue at two-year intervals thereafter.

And I think since that's one of the questions before the Panel, it may be interesting to consider that we actually do have the estimated rupture rate available from the core study at three years. For the primary augmentation cohort, which is the largest group of patients to receive these implants, the suspected or confirmed rate of rupture at three years is 0.5 percent.

Now, patient compliance, as was mentioned in the previous presentation, is something that's being tracked in the large postapproval studies to see what percentage of patients are actually following those recommendations. And as was mentioned earlier, we now have data through three years, so they're really just now reaching the interval where they would start implementing those recommendations.

Now, for patients who do have three-year follow-up, compliance is low. Less than five percent of patients in the large PAS have

had an MRI.

Now, because of the reasons listed above here, a number of surgeons have recommended that it may be appropriate at this time, based on the new information we have, to revisit those recommendations. And we would certainly concur with that view.

Now, one of the main experiences I think that we've had with the large postapproval study -- and this was mentioned in both of the presentations earlier -- is achieving adequate follow-up rates.

Now, FDA sponsored a workshop on postapproval studies back in the summer of 2009, and at that workshop Todd Fonseca, from Medtronic, noted that one is designing these postapproval studies, the greater one deviates from standard clinical practice, the greater one would expect the challenges to be. And three of the points that he highlighted were frequency of follow-up that was not part of some standard practice.

Now, if we consider the breast implant patients, follow-up past one year is not typical practice for most patients who receive breast implants. By that time they're fully healed from their surgery, and if they don't have problems, they often do not return. And that's quite distinct from a patient with a heart valve, who would be expected to return regularly over a very long period of time for follow-up of their medical condition.

The second challenge is, if the procedures or assessments go beyond standard practice, that would represent a potential issue. If we look

at the breast implant patients in these studies, in the large postapproval study, the questionnaire is 27 pages in length, and some patients have used the terms arduous or intrusive to describe that questionnaire. Now, about 40 percent of that questionnaire is collecting covariates to help interpret the results, but certainly the thought is that the length of the questionnaire contributes to the compliance issue that's being seen.

And, third, with respect to length of study, the 10-year duration of the large postapproval study certainly extends well beyond standard clinical practice.

Now, interpreting the follow-up of breast implant patients and the patients -- how one would view the patients who don't return for follow-up, Dr. Leroy Young and colleagues, back in 2004, published a survey that they did, and one of the things that survey explored was the reasons why women did not return, either schedule or return for follow-up appointments that their surgeons recommend, and the key finding was that the main reason for noncompliance was an absence of problems with the implants. So I think for this patient population and the discussions to follow in the next two days, I think that's a useful point to consider.

Now, with the large postapproval study, when the potential issue of low follow-up was first identified, Mentor met with FDA -- and I think we'll be hearing more from FDA on these measures in their presentation, from what was said. But the Mentor team worked with FDA to try various

measures in an effort to increase those follow-up rates.

These included having "Dear Patient" letters sent to the patients from their physicians. Mentor initiated the development of a letter from FDA that was sent to investigators. A similar letter was sent to more than 40,000 patients. And these letters from FDA communicated the importance of the study, the importance of the data to be gleaned from the study, and really encouraged the ongoing, active participation of both patients and surgeons in these studies.

Following some feedback on the website, the website was modified and updated. And then also Mentor initiated and helped facilitate FDA participation in sessions at the National Plastic Surgery Society meetings, again, to encourage and reinforce physician involvement to increase patient follow-up.

Yet despite the implementation and the measures that you see on this slide, none of these really seemed to move the needle much. And so there's ongoing discussions with FDA on further measures in terms of how to address the follow-up issue in the large postapproval study.

But as we view the objective of today's meeting, one of the other objectives was to look forward, and what we'd like to do in the remaining time is really turn our attention to science-based approaches for postmarket studies of silicone breast implants in the future.

And some key principles have emerged from the observations

and experience we've had today. First of all, if one looks at that original list of objectives for the large postapproval trial, one can address those individual objectives with different numbers of patients for different objectives and from different data sources. For example, certainly one doesn't need as many patients to track more common local complications as compared with the more rare health endpoints.

And we think also that this is an excellent opportunity to stop for a moment and really critically evaluate whether some of those original objectives, the original endpoints, are already addressed through the findings of expert panel reviews and from the extensive body of literature available containing epidemiology findings. And this focus would then allow resources, where we're talking about FDA, sponsors, the time and effort of physicians and patients, to be targeted to those remaining endpoints in an effort to optimize the likelihood of success.

Now, here you see listed the 12 original objectives of the large postapproval study, and in the following slides what I'd like to share with you are some alternative data sources to address, in a composite, all of these 12 objectives.

Now, there's a myriad of data sources available. There's the information we have from the ever-expanding medical literature, both existing and ongoing monitoring going forward; the findings of multiple expert panels; continuation of the prospective core clinical trial that you

heard described earlier. The term core is a regulatory term. In this case, referring to the primary IDE study that's used to study breast implant patients, typically includes the four cohorts that were described earlier this morning.

And then continuation, where it's available, of the prospective continued access studies, also out to 10 years. The continued access studies represent studies where, once the targeted enrollment is complete for the core study, additional patients may be enrolled into such a continued access study to collect additional adverse event and complication data to inform the regulatory review process.

We also have registries. There's quite a list of those in the FDA Executive Summary, as well as something I think you'll hear later about in this meeting, the TOPS registry run by ASPS. Also administrative health databases offer a potential source, and we'll be saying a little bit about postmarket surveillance data.

Now, in addition to those which will be the focus of the meeting today, we're also very actively tracking some very promising initiatives, and we really look forward to seeing the outcome of these efforts. These were mentioned in this morning's presentation, the MDEpiNet and the Sentinel Initiative. And the hope is that, going forward, these may provide some truly innovative approaches that may address some of the issues that have been seen with the current studies.

Now, with the breast implant patients, perhaps the greatest challenge in using a lot of the resources that have been proposed is identifying the patients within those various data sources because most women who receive breast implants, their initial surgery is not covered by insurance. So identification of the breast implant patient is a challenge.

What you see represented in this table is a summary of the approach going forward. On the left-hand side you see the 12 original objectives, in addition to effectiveness listed there at the bottom, and then the various sources that we talked about on the previous slide and how they relate to the various objectives.

So first of all, if we focus on local complications, signs and symptoms, mammography, MRI compliance, and effectiveness, the recommended approach would be to use the core and core continued access study data going out through 10 years.

With respect to the longer-term health conditions such as connective tissue disease, neurological disease, and the others you see listed here, the recommendation would be that those are addressed by expert panel findings, the literature, registries, and meta-analyses.

Now, one of the things that's typically brought up when everyone's talking about postapproval studies is real-world experience, and the objectives of postapproval studies very oftentimes include evaluating real-world and long-term performance of devices after market approval. And

if one looks, for instance, on the FDA website that tracks the progress of postapproval studies, I thought it would be interesting to look at the PMA approvals that corresponded with those postapproval efforts and look at how many clinical sites were involved in the pivotal trials for those PMAs.

And in looking at quite a number of those, what was seen is there were numerous examples in which the total number of study sites was below 20. In some it was as low as two sites, and again, not geographically distributed. And in that type of situation one really, I think, has a very appropriate question to ask. Once the device is introduced to a much larger number of surgeons, would one expect to really see the same complication rate? And I think it's a very important question to ask.

In the case of the MemoryGel core study and the core studies for these devices, it included 41 sites that were geographically distributed across the United States and a range of different practices. It was primarily private practices, which represents the current practice of plastic surgery, where it's estimated that more than 50 percent of plastic surgeons are in solo practice. So these are not highly specialized academic centers where one might expect a different degree of results.

So we think that one possible consideration might be that if this was considered in the design of core studies going forward into the future, and one ensured that there was geographically diverse sites with demographically representative surgeons, this might collect the real-world

experience and obviate the need to address local complications, which is really the objective that relates to real world going forward.

Now, next on the list was connective tissue disease, and connective tissue disease has been addressed in some depth by a number of expert panels. Listed on this slide are the Independent Review Group, the National Science Panel, and the Institute of Medicine.

And if we look at just one of those, the Independent Review Group, they concluded that there was no epidemiological evidence for any link between silicone gel breast implants and any established connective tissue disease. And they even went so far, based on the body of evidence that they reviewed, to conclude that they could not justify recommending further epidemiological studies to investigate that hypothesis.

Now, the use of expert panel data and the use of literature is certainly consistent with FDA guidance, and as you heard in one of the presentations earlier this morning, it certainly informs our knowledge about the safety and effectiveness of these devices.

In the very recently released 522 postmarket surveillance guidance, they pointed out, in terms of determining which studies should be done, one of the questions one should ask is, is there any other source of data that may be used to address the public health question? And literature was one of those sources that was specifically named.

Also, if we look at the breast implant PMA guidance, it

addresses another issue with literature, which is literature is not always going to contain just information or focus on solely one manufacturer's device. But there's certainly precedence for pooling data for different devices if the similarities are there.

Now, another question that arises on literature is, if you look at those large epidemiology studies on breast implants, quite a number of the patients in those studies had earlier-generation breast implants. So how does that information relate to what we have now? And how appropriate is it to use that information to evaluate the risk of the current devices?

Well, if we look at the situation there, a significant portion were the generation two devices that preceded the ones that were approved in 2006. These went off the market in the late 1980s and they have high levels of gel bleed, very high levels of rupture. So from an exposure standpoint, patients who had those implants had much higher levels of silicone exposure than current patients.

So if one doesn't see a safety signal in that data, it actually provides an added margin of safety for those health endpoints in considering the current devices. So for those endpoints, I think it's quite appropriate and relevant.

Now, if one's considering an issue such as rupture, though, that certainly is dependent upon the mechanical characteristics of a particular manufacturer's device, and in that instance, I think one certainly wants

postmarket data or long-term follow-up, specifically on a given manufacturer's device.

Now, connective tissue disease has been addressed by a wealth of published literature. You see most of those represented on this slide. It's a combined total of more than 38,000 unique patients, addressing a number of different connective tissue diseases.

I wanted to also present an example of the potential effects of offspring, as it's captured in the published literature, because this, I think, is an example where some of the information from these studies actually represents a much more powerful study design than is probably possible to execute here in the United States.

These studies were from the Scandinavian countries with national healthcare systems, and they were able to use the national population registers to identify all of the children born to women with breast implants. And then, in these two largest studies, which had the best design, they were actually able to compare the incidence of adverse health outcomes in children born to those women before they had breast implants and born to the same women after they had breast implant surgery. And what they found was either lower or no difference in adverse health endpoints in children born after versus before cosmetic breast implant surgery.

Another strong example comes to us from breast cancer. If we dial back a few decades, the issue of breast cancer was one of the very

important questions being considered with respect to breast implants and their potential impact. We now have the results, reflected on this screen, of the five most recent large epidemiology studies on breast cancer among women with breast implants.

And what we see is these studies represent data from studies from five different countries. It represents, combined, more than 625,000 patient-years of follow-up. All five studies identified a reduced risk of breast cancer for women with breast implants, and the three most recently conducted studies all found that that reduced risk in breast cancer was statistically significant.

Now, the other endpoints listed on this slide are also addressed by a considerable body of literature, and some of the sample references are reflected here.

The next topic I wanted to cover is enhanced postmarket surveillance. If one looks at FDA's listing for postapproval studies and their status, there's at least six examples there where this enhanced postmarket surveillance is being used as one of the postapproval study requirements, and that includes devices in the cardiovascular field, in the orthopedic field, and in urology.

DR. LoCICERO: You have about two minutes left.

DR. WIXTROM: Okay. The objective here is to identify trends and safety signals both to address -- to identify public health questions. And

this involves monitoring the complaints and adverse events data, both MDR and non-MDR data, then tracking the usage through the device tracking database to provide some sort of magnitude with a denominator and then actively monitoring the published literature and published case reports, where if one sees a potential signal there, one can then go back and look in the complaints, adverse events, and link device tracking data to see if it's reflected there.

And consistent with what you heard in one of the earlier presentations, one can then have as an output the identification of potential safety signals, which can then lead to design very targeted studies to look at any of those identified signals.

Now, this is the last slide of mine before turning it back to Dr. Canady. And I think it's useful when one's considering postapproval studies and proposed designs to ask the question, would that proposal be able to detect rare signals? And I think we have the answer in the case of ALCL.

ALCL, as it turns out, was initially identified by case reports in the published literature. That was followed by an epidemiology study published in the Netherlands. Further case reports emerged, which led to more detailed investigation regarding the characteristics of both the patients and the implants, which then led to the manufacturers checking their databases for occurrence and submitting that data to FDA and to the

researchers in this area.

An expert panel was convened and the findings of that expert panel was then used to inform the regulatory agencies, and FDA issued the advisories that you heard described earlier. And now there's an establishment of a registry through a collaborative effort of FDA and the plastic surgeons. And so this is an example where that was successfully incorporated.

So I would just like to turn it over to John for closing comments.

DR. CANADY: Thank you, Roger.

Through this presentation we have shown the evolution of our thoughts about postmarket studies and our focus on patient safety. And in our final slide, in summary, I think, in our view, many of the objectives of the original large postapproval study have been addressed by literature, registries, and expert panels.

Core and continued access studies should be continued through 10 years to provide both long-term outcomes and real-world experience.

Enhanced postmarket surveillance is recommended to detect safety signals and public health issues. And if safety signals are identified, Mentor proposes designing and implementing targeted studies in collaboration with the FDA.

Thank you very much.

DR. LoCICERO: Thank you. I'd like to thank both of the

sponsors for their thorough presentations. And in preparation for the Panel to begin asking questions, I would like both sponsors to prepare an answer to the following.

When we do studies, after they're completed and we're writing it up in our discussions, we often list our design flaws, what our problems were. It's sort of a self-assessment of our own work in a critical way. So I'd like both sponsors to prepare three bullets as to what they think the design flaws' impediments to drawing conclusions or confounding issues were. I understand that you presented a lot of discussion, but I'd like this in a succinct manner so it will allow us to focus our discussion better.

So now I want to open it up to the Panel for other questions, please. Anybody. Okay.

DR. HONEIN: Peggy Honein with CDC.

I have a question for both sponsors on what incentives were offered and what creative options for different sort of participant choice and the incentives that were attempted to increase participation, and if there were other efforts, such as newsletters or testimonials from people that were very committed to the study, that were attempted to increase participation.

DR. LoCICERO: Either of you can jump in.

DR. AVELAR: Rui Avelar, Chief Medical Officer for Allergan.

When we started, we started with some cash incentives, token amounts. It was $10 and it was increased to $20. And then for when --

following enrollment there was $100 payments for the office visits in year 1, 4, and 10, to compensate people for time lost from work and to come in. And there were also obviously the mailings that went out to try and categorize people to come in, to try and bring them in.

And when we talk about incentives, it may not be completely on the point, but one of the important parts was we really tried to appeal to their sense of there was a mission here, there was a sense of commitment to trying to increase the body of knowledge. So the whole concept of that logo that I put in, the power of one and how it impacts many, we really did try and brand that and bring that symbol up, to bring that up as an incentivator to bring people in.

MS. SELLEY: Yes, good morning. This is Nicola Selley. I'm with Mentor.

Mentor actually determined not to offer incentives for the large PAS. We had initiated a mandatory study initially, and for patients and physicians, and later on we did remove that restriction and make it voluntary for patients. But in hindsight, we believe that we -- as keeping the mandatory for physicians, that we lost some of the willingness to continue participation and, you know, we have resulted in a low follow-up rate, which we're obviously very, very disappointed in.

We have been in discussion with FDA on methods to improve the follow-up. Incentives are certainly in consideration. But to date, in this

PAS study, we didn't offer any incentives. We did actively try and contact patients four weeks prior to their anniversary for filling out the questionnaires, two weeks and one week, and then if we didn't have a response, we would contact them again at four weeks and at seven weeks. Thank you.

DR. LoCICERO: Dr. Leitch.

DR. LEITCH: From the physician perspective, what was the compensation for patients participating in the study and follow-up visits?

MS. MONROE: Rose Monroe, study manager for the BIFS program.

There is no compensation to the investigators for the 1, 4, and 10-year in-office visit currently. At enrollment, the investigators received up to $200 for the enrollment of the patient.

DR. LoCICERO: Mentor.

MS. SELLEY: Yes, at enrollment, our physicians received $100 for enrolling their patients, and following that there has been no additional compensation.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: Could we ask the two manufacturers to comment on the expense of MRIs, the costs to patients for these, and how this has been handled to try to help these patients move forward with getting MRIs?

DR. LoCICERO: The mike, please.

MS. SELLEY: Sorry. Yes, for the MRIs, the average cost for patients is anything from $1500 to $2500. And for our core study, we do offer -- we do pay that for our patients. But in the past we have not.

DR. AVELAR: For the Allergan study, similar. In the core study, the sponsor paid for them, and in the BIF study, the patients were responsible for it. The average costs, similar, in about the $1200 to $1500 range.

DR. LoCICERO: Dr. Vega.

DR. VEGA: I'd like to ask -- first of all, I'd like -- we'll try again, all right? I'd like to have a question develop between both companies, and that is about the cultural sensitivity and diversity and how that is addressed, because having spoken in many different Latin-American countries, et cetera, I can tell you that it's very obviously difficult to have patients come forward in your studies. However, I'm wondering what you do specifically to help patients so that they're feeling more comfortable in their own cultural bases and background.

DR. AVELAR: For Allergan, there was a very large representation of Caucasians; I believe about 15 percent Hispanic and about 5 percent Asian. So really those were the three most prominent. And basically, the best way that we found to address that was to respect privacy.

So we tried to hone in on the individual patient and what medium would they prefer to communicate with, so that they had a sense of

-- set up an environment where they could be most comfortable, so some by e-mail, some by phone. Now, did we specifically create an environment that addressed the different ones? I'm not aware of one.

I was just going to add one more thing. I didn't put it up in the original slide, but, for BIFS, you needed to be fluent in Spanish or English, and from a cultural perspective, the one thing that we did have was -- to facilitate the Hispanics, was to have Spanish translation.

DR. WIXTROM: And actually the answer from Mentor is very similar to what you just heard, and the forms were translated into Spanish to reach that population.

And actually I would say, even beyond the studies, one of the ongoing issues in plastic surgery, particularly for breast reconstruction patients, is recent studies have shown that many patients, and actually a higher percentage of minority patients, actually are not even given information about the options of breast reconstruction. So there are certainly efforts underway that Mentor is supporting in that area, too, even beyond these studies.

DR. VEGA: I think a very, very important piece would be for both companies to understand that testimonials of another person who is what I call a comadre --

DR. WIXTROM: Right.

DR. VEGA: -- a significant person in the community who is

exemplary, would be a wonderful, wonderful thing and very helpful, I believe. I'd be happy to discuss that with you. It's called the Comadre program, and I think it's probably a very big aid, or would be a very big aid to facilitate more participation.

DR. WIXTROM: Right. And I think in some of the online materials for breast reconstruction patients, they've included some testimonials. But I think enhancing that, I completely agree, that's worth emphasizing.

DR. LoCICERO: Are either of the sponsors prepared to give their bullets? Mentor.

DR. WIXTROM: Okay. So if I heard you correctly, the question was, if one was writing a portion of the scientific paper on design flaws of the large postapproval study, what goes there?

I think, first of all, in retrospect, the long questionnaire. Mentor has, as was mentioned earlier, the 27-page questionnaire. There's thoughts right now even as far as potentially reducing that. Some of the covariates that were collected at baseline, perhaps, I mean, one would like to get those every follow-up visit, but maybe now it's not so essential. So I would say that, I think, among the team is one.

You heard mention that, you know, it was actually for historical reasons. Going back to some of the earlier breast implant studies, back for the saline breast implants, there were issues with successfully achieving

enrollment of those patients. So that's why Mentor opted for mandatory enrollment following approval, and the thought there was that by making it mandatory, in order for patients or physicians to have access to these implants, they would have to enroll in the study. That enrollment then would occur in a much more timely fashion. You know, in that aspect, it was successful. Mentor did complete its enrollment earlier.

But I think, in retrospect, it's perhaps not surprising, thinking back, that if a patient or a surgeon enrolls because they have to, they're required to, and that that patient, as part of informed consent, is told that they're free to discontinue from the study at any time point, I think it's probably not surprising that that might contribute significantly to low follow-up rates. And I think the value and benefit of voluntary enrollment is something that's certainly been highlighted quite strongly. Unfortunately, that's something one can't go back, you know, and redo for that study.

And then the third one that I listed is maybe an overreach in the design of the study. And I think when we talked about, in today's presentation, the alternative data sources for addressing some of the endpoints, I think, in retrospect, if there would have been opportunity to maybe explore that, and I addressed different endpoints with different data sources and a different number of patients, that may have enhanced success.

So just off the top of my head, that would be the three initial design flaws that would come to mind.

DR. LoCICERO: Thank you. Is Allergan ready?

DR. AVELAR: So Allergan, a fairly similar response. I think number one was there was probably an opportunity to pool the data. If we look at what we're trying to do, consistent with what Mentor just said, we were perhaps a little bit ambitious. And we know that we can pool data, but I think we can also be respectful of the differences and track the different manufacturers and look at what is relevant, what is overlaps and what is unique to each one.

I think the second one really is the questionnaires. We all try with good intent and we're all trying to collect quality information. But as I mentioned, there's a diminishing return. The more you ask, the more you disincentivize patients. So although with good intent, patients reach a threshold where they no longer want to participate or they just give up on a questionnaire.

And then the final one is really just a practical one. This is a really large study, and I think one of the things is we may have asked for too much. If we look at the size of these studies and we take into consideration how many patients are involved, how many sites are involved, the order of magnitude to get that done, and then if you look at the pool of patients that are available annually, there's only about, you know, 300,000 augmentation patients and about 100,000 reconstruction patients. If you try to put that all together, it really does present a challenge.

I presented to you a compliance rate of 37 percent, but that's where we are today, and despite our best efforts, you know, we don't know where that ends up later.

DR. LoCICERO: Dr. Connor.

DR. CONNOR: So this is a question for Mentor. And first I thought Dr. LoCicero's question was going to elicit this, but then when you said the third point was overreaching, I thought I'd ask anyway.

So one of the reasons for your low follow-up rate that you mentioned or you cited -- and we appreciate that these are hard studies. When I buy a product, I hope it works, and I never have any contact with its maker. But you cited the postapproval conference at FDA and the gentleman from Medtronic saying one of the difficulties is anything that's beyond the normal course of care, any studies or any visits, lead to follow-up rates being lower.

But you also mentioned that the last typical follow-up visit was at one year after an implant surgery. But even your rate at one year is just 21.8 percent, which seems embarrassingly low, and that seems to be within the normal course of care.

So I wondered if you could say, you know, why that's so much lower. And it's three times lower or Allergan's is three times higher than yours.

DR. WIXTROM: I guess in response to that I'd say it's

interesting to look, I think, at the core study where we had one-year follow-up rate which was extremely high, and then, in the postapproval study, one sees the very low rate, you said.

And also consistent with what you saw in the Allergan presentation, if you actually look at those numbers for augmentation patients and reconstruction patients, it's about a 50-percent higher follow-up rate in both studies, in terms of compared with augmentation patients. So they have a little more reason to come back to their surgeon.

But I would say the thought of those -- you know, the experts have looked at to this point -- is that really probably the number one factor in really the follow-up in the postapproval study is that mandatory enrollment and the fact that the thought of some that if I sign up for this study, I can get the device, I can just discontinue from the study, and that certainly would seem to be reflected in those rates. So I think that's a very powerful lesson learned going forward.

DR. LoCICERO: Ms. Dubler.

MS. DUBLER: I'm struck by some of the explanations that have been given and some of the words that have not appeared. So incentives have a bad reputation in research because it is claimed by some people that they "are coercive." I don't think incentives are ever coercive, but an incentive that's overly generous might in fact cause a patient to neglect self-interest. But I don't think that's a factor here. So incentives by and large

work, is what the research literature shows. And I think that's important to note.

The word that I'm missing is altruism. So patients who care about what they're doing often care about the cohort that they belong to, and the notion that women might want to help other women by learning things is a powerful one that hasn't appeared here.

I'm especially concerned about the re-surgical rate and the capsular contracture rate. The latter seems to remain stable, and the interesting thing to me about the re-surgeries are how many are requested by women themselves. I mean, that's truly interesting. And it would seem to me it would be a great incentive to women to help them to hone their own personal intellectual calculus so that they would be less likely to come back and request surgery.

So I think there are some very interesting approaches to incentives which I haven't heard mentioned, and I wonder if either of the companies considered any of those approaches and used them to any degree, and did they succeed or fail.

DR. WIXTROM: I guess the part of what you said, I thought, might be worth sharing some information on is you said that one of the things that surprised you, and I think surprised a number of the people reviewing this data, were the number of reoperations requested by patients, and that's something that both manufacturers, and actually surgeons from the societies,

have taken very serious interest in addressing. And since most of those patient-requested reoperations were due to size change, both companies have sort of supported more rigorous or scientific approaches to selection of a particular implant that's optimal for that patient.

So there's two different systems. One is called the 555. Actually the author of that system is a surgeon here today. And then the one that Mentor developed through an international group of surgeons is called the BodyLogic System. And it incorporates body measurements and the thought is that, for a given woman, when you're talking about augmentation or reconstruction, by evaluating that woman's tissue characteristics and body characteristics, one can select an implant that's best suited, you know, for the best results, not just immediate, but over the medium and long term in that.

And so those efforts have been put into place, and included in that -- at least I know the BodyLogic, I'm a little more familiar with that -- also includes more specifically addressing patient expectations at the time of the selection of that original implant and really making sure that what the surgeon is doing is matching those expectations.

And actually there is a study that's been designed -- I don't think we have the results yet from it -- which was aimed at looking by implementation of the BodyLogic System by surgeons, will that significantly reduce the patient-requested reoperations? But I hope in the not too distant future we do have the results because I think most people are feeling, you

know, those are things we should be able to avoid.

And then just really quickly, I'll say the other one was the issue of capsular contracture. That's something I personally have focused on and provide lectures to plastic surgeons on. There's a lot of research and effort underway to better understand the causes of that, which may not be so directly related to the device itself, and measures that can be implemented at the time of surgery to reduce that incidence.

So that, I would say, is one of the most active areas of investigation because that's another one. That's a clear target to substantially -- wanting to substantially reduce complication rates.

DR. LoCICERO: Follow-up?

MS. DUBLER: I'd just like -- oh, I'm sorry, go ahead.

DR. AVELAR: I was just going to chime in on your question. Just to go back to the altruism, that was actually one of the big thrusts of the Allergan -- sorry. Allergan, Rui Avelar, Chief Medical Officer. That was actually one of the big thrusts in our program.

That symbol that I put up that spoke to the power of one, strength of many that was the whole idea behind it. And the concept of listening to the individuals who participate in the trial, listening to -- one of the big motivators was, if you help us with this study, we'll all learn. We will be able to educate, we'll be able to learn from this process, then we'll be able to share this information and bring that data together and then again

distribute it in many different ways.

On the capsular contracture side, I'd like to introduce Dr. Scott Spear -- he's known to the FDA -- a plastic surgeon here in Washington and one of the PIs in the study.

DR. SPEAR: Thank you, Rui.

Just to speak to the reoperation rate, this has been a thorny subject and I think the Panel kind of got its hands around it earlier today when -- it just collects a lot of information, some of it relevant, some of it not relevant. But the reoperation rate for capsular contracture is about 25 percent of all the reoperations. So at 10 years it might be at 5 or 6 percent of all the patients, which we believe is a low number for a device problem at 10 years, if it is in fact device related.

Regarding the other elective changes, first of all, women's bodies change over those 10 years. So one issue is that what was appropriate at 25 years of age may not be as appropriate at 35 years of age. So some women do change and change for a size larger because they underestimated how much they would like that change. Some choose to go a size smaller as they get older. So I think, biologically, women's bodies don't stay the same over 10 or 20 years either, so the device is meant to sort of fit the body.

And then the last thing I'd say about reoperations in general is that it's become a concern for the manufacturers because it doesn't look good. And so I think there are efforts, particularly in terms of what's under

the surgeon's control, to try to become more accurate and more precise, more wise about what needs to be done.

But at the end of the day, particularly in the augmentation patient population, it's an elective operation and so there are changes in taste or judgment that occur. You know, I don't think we want to be in a position of telling women they can't have a change of mind. So whether they want to go bigger, smaller, or remove the device altogether, I think it's a personal decision. So it's never going to go to be zero. What we'd like to do is reduce the number.

And I don't like the language, that women have to have another operation, because there are very few that actually have to have another operation. A lot of these decisions are judgmental and elective.

DR. LoCICERO: Follow-up?

MS. DUBLER: I thought those were very interesting and helpful responses. I would just follow up with one more set of concerns, and that is, when we talk about physicians and patients, we're talking about very, very, very different groups. So it's totally appropriate and demanded by research ethics that patients be told they can drop out of a research study at any time. On the other hand, it's equally appropriate to say why it would be important for them to stay.

For physicians, I think it's really quite different, and if you have a physician with just an extremely low participation rate, it may be that that

physician doesn't get any more product to use. Now, that is a bit coercive, but I don't see any reason why it's not appropriate. So patients are one cohort, and we need to attract them and entice them. Physicians are another matter.

And, finally, I don't see why any woman would pay out of pocket for an MRI. I just don't see it. If you want women to have MRIs for a study, you have to pay for them.

So given those rather nit-picky comments on your very excellent presentations, I think there are some very strong measures that could be taken to move the study forward.

DR. LoCICERO: Thank you. Dr. Mount.

DR. MOUNT: I just wanted to make a clarification. Perhaps, Dr. Spear, you can answer this question. The clarification is with the size change. The request by patients for either upsizing or downsizing, is that unique to silicone breast implants or is that potentially an issue with all breast implants, including saline? My impression was decisions change as time goes on, and this would not be something particular to a silicone implant.

DR. SPEAR: I think it's true of all breast implants, silicone or saline.

DR. LoCICERO: Dr. Leitch.

DR. LEITCH: I wanted information about the compliance with

getting MRIs in the core study, where they were paid for versus the non-paid for, for each group, Allergan and Mentor.

DR. AVELAR: Allergan, Rui Avelar.

The final results and the exact numbers for core have just been compiled and they've been brought in, and I don't have them on the top of my head, but it comes in in the 80 percent category. Eighty percent, eight-zero. And that was compensated; the BIF study, which is again postmarket, and the objective there that speaks to your point to a large extent is patient compliance. So the label says that patients are to have these, and here are the recommended time intervals.

So in the real world, if the BIF studies reflects what's happening in the real world, then patients have to pay for it. It's early on, but I think the compliance is under five percent right now, and I can confirm that for you as I look at it.

DR. LoCICERO: Does Mentor have any numbers yet? While you're trying to get those, Dr. Callahan.

DR. CALLAHAN: Do you have information on the socioeconomic status of your participants and the rates of follow-up according to SES levels and also rates of follow-up according the different ethnic groups? And as well, rates of compliance with the MRIs in those groups.

DR. AVELAR: So the 10-year data has been submitted. I don't have that with me. We didn't stratify by socioeconomics, so I don't have that

answer for you.

DR. POGGIO: My name is Gene Poggio. I'm a statistical consultant to Mentor.

For the large PAS, the large postapproval study, we were interested in whether there was any evidence of participation bias due to the low follow-up and potential for bias. And so we compared the demographic and surgical characteristics at baseline for those who participated as compared to those who didn't.

There's obviously a huge sample size. From a statistical point of view, tiny differences do get detected. So we do have a number of statistically significant differences, but I would say that most clinicians would think the differences are not clinically significant. As an example, for primary aug, the age difference between the two was approximately two years, but highly statistically significant.

So in looking through them, many of them weren't statistically significant, but nothing was very large. And as I said, we compared both demographic and surgical characteristics and input characteristics as well.

DR. LoCICERO: Dr. Mount.

DR. CALLAHAN: And follow-up -- and loss to follow-up?

DR. POGGIO: This was comparing those who didn't participate -- I think this was the two-year time frame -- compared to those who did, comparing the surgical and the baseline characteristics.

DR. LoCICERO: Okay, Dr. Mount.

DR. MOUNT: Del Mount, Madison, Wisconsin.

I have a question about the core study, and actually it is a question that really revolves around MRI. I mean, I will compliment you both on having very high enrollments on that. I think this is very statistically powerful.

My question is, if a patient enrolls as a primary augmentation patient and they fall into that category where they have an MRI that shows rupture, do they then get placed back into the revision augmentation category? Do they get reenrolled into that group, or are they followed differently than a patient that has been in the primary aug group with this recommendation of one, three, five years as far as their MRI goes? And are the subsequent MRIs, after a rupture, do they give you the same information or as reliable of information about rupture for potentially a second rupture?

DR. AVELAR: So for Allergan, to limit confusion, primary augmentation patients stay within the primary augmentation. We have specificity/sensitivity data on the MRIs that have been generated.

In terms of the implication of what is the sensitivity or specificity after, I don't think we've cut the data that way to look at it. The suspicion would be that it would revert back to the same because you're not really leaving any other foreign bodies and the scar tissue that'd be there really shouldn't be a confounder, if you look at the landmarks and the kind of

signals that you're looking for that typically signal a rupture.

DR. MOUNT: And have patients that have gone back for removal of the implant undergone a capsulectomy in its entirety or just replacement of the implant for those subsequent MRIs?

DR. AVELAR: Sure. So I don't know if Dr. Spear would like to add, but if we look at patients who underwent a removal, over 90 percent of them had a re-implant.

DR. MOUNT: Again with silicone? Or what are the numbers that shows silicone versus autologous versus saline?

DR. AVELAR: Most of them would be in the silicone. In fact, some of the prior experiences that we've had where we've seen capsular contractures with saline, they've actually, when they've gone through the explant, had a silicone put in after the saline.

DR. POGGIO: Gene Poggio again.

Just on the first part of your question, Mentor also kept patients assigned to the original cohort for the duration of the study. Also one should keep in mind that often the patient is getting two implants, and a change in status in one wouldn't necessarily change the other.

And in fact there is a slightly different classification. We do analysis at both the patient level and the implant level, and the implant classification is slightly different. For example, a woman who has primary reconstruction in one breast and augmentation in the other. For implant

level, those are the two classifications. But for the patient classification, that patient is considered a reconstruction patient.

DR. SPEAR: And just to follow up on the MRI, for the positive MRIs, it was the physician's discretion whether a capsulectomy was done or not. But I think, in most cases, the capsulectomies were done in the case of a positive MRI, and there's no reason why a subsequent MRI in that patient should not be just as accurate as the original MRI.

DR. LoCICERO: Dr. Jones.

DR. JONES: So I'm interested in the BIF website and access to peer-to-peer interactions maybe that could encourage the patients to comply. Were patients able to communicate with each other on the website?

As a separate question, are there other sites that have formed sort of spontaneously, women in these groups who are interested and passionate about the difficulties that they're having?

MS. MONROE: Rose Monroe, Allergan.

Very good questions. Actually, when we went to revise the BIFS website after we conducted the focus groups, we asked the participants at the focus groups, what do you want to see? What information do you want access to? And confidentiality was actually a big part of their concern. You know, Facebook. Do you want a BIFS page on Facebook? They don't. This is a very personal decision even in our augmentation group. They don't want to be out there discussing this with women they don't know. That was

our findings as far as the focus group was concerned.

With the website particularly, we changed the messaging. It's available to our investigators as well as to the participants. The participants log in to complete their annual questionnaire. They receive e-mails where they can click on a link, go directly to the EDC login page, enter in a couple factors, and get right into their questionnaire. They also have the ability to make appointments to complete the annual questionnaire with the call center via phone.

We've come a long way with that. I think we've made it much easier for the participant to complete an annual questionnaire. They can still complete it via paper, though very few do.

When we started the study, I think it's important to note that our assumptions weren't correct. We assumed that 80 percent of the participants would be completing the questionnaires online. That was absolutely not the case. It was more like 40 percent. So immediately we made the change to increase the personnel in our call center to address that issue.

But then the long-term solution. What do we need to look at? What's the root cause? Why aren't these participants completing the questionnaire online? It's so easy. Click, click, click, you're done. I think what we did after the focus groups is we made a lot of different changes to address that, not only in the messaging, but the ease of getting onto the

website, the questionnaire, building in the skip logic that makes it that much more simple for the participant to go through the questionnaire in the safety of their home, for example.

Does that answer your question? Thank you.

DR. LoCICERO: Yes.

MS. MATTIVI: Kris Mattivi. I'm the Consumer Representative.

Along those same lines, I know, in our work as the quality improvement organization in Colorado, we've learned that as far as sustained engagement in any campaign or in any effort is a challenge, and certainly having patient champions and physician champions in our work with physicians has been extremely important. So I'm pleased to hear about what you've done with the website.

Allergan indicated that they had increased the financial compensation to the patients, and I'm wondering if that made any difference. Did you track? Which of your interventions actually made a difference in your patient engagement, in your physician engagement? Were there physician champions out there as well? So I'm interested to hear some of that.

Oh, the other thing that I wanted to say is I'm not surprised -- I'd be interested to hear from Mentor if the letter from the FDA had any effect on patient engagement or physician engagement. Again, in our experience with -- it all comes down to having a relationship with the

organization. I'm wondering if a letter from the FDA really had much of an effect.

MS. MONROE: Rose Monroe.

I think you bring up a good word there, relationship. The key thing with this BIFS program is that we're developing a relationship with 57,000 women across the United States. We not only need to develop that relationship, but we need to maintain it for 10 years. A huge task.

So to your question, I think there's some opportunity to more involve the physicians, absolutely, especially with the 1, 4, and 10-year visit, and we've made strides to do that ourselves at Allergan. We are sending out compliance packets to the investigator, making it that much easier for them to log in to the registry system as well, our EDC system, to see when are your patients due? What are the windows? What can we do to help you to get that patient in?

But not only that, our outreach algorithm. We start reaching out to the patients early on. As soon as they enter their window, we're reaching out to the patient to say, hey, it's time to complete your annual questionnaire. And the algorithm includes e-mail, IVRS, a live phone call, mailings. And I think, as far as our engagement with the patient, that has done wonders.

You mentioned, have we looked at what initiatives have made an impact? Absolutely. When we conducted the focus groups and made

many changes not only to our logo and to the messaging and to the website, the online completion of annual questionnaires increased considerably. They doubled, and it exceeded our expectations, basically. So we were very pleased with that.

Financial compensation absolutely made a difference. We started out, as was mentioned earlier, with $10 per annual questionnaire, and we upped it to $20, and that was actually done in the first year. We did see some difference in that, but I think what we learned from the focus groups was that yeah, the $20 is fine.

What other type of compensation is out there? We wanted to know. Do you want a gift card? You know, is there something else that you offer? Do you want to get cold, hard cash? And in these cases they wanted to see that money, but it wasn't the largest factor. Important, yes. But $20 is fine. It's really more about my responsibility as a participant in the study.

DR. CANADY: John Canady for Mentor.

With respect to the FDA letter, although it seemed like a good idea when we thought about doing it, it did not have any effect in terms of response after it was mailed out.

DR. LoCICERO: Ms. Dubler.

MS. DUBLER: Nancy Dubler.

Just to follow up on the confidentiality issue for a minute. We all learned during the early years of AIDS that letters and phone calls and

e-mails that could be recognizable to others was a real problem for our patients, and these women seem to be very concerned about maintaining confidentiality.

So to Allergan. When the letters and phone calls and e-mails go out, are they identifiable as coming from you?

DR. AVELAR: Allergan.

Yes. And if you remember the logo that I posted up, that's why that was put there, to -- you know, the naiveté, they probably wouldn't recognize what this stands for, they wouldn't understand what that logo stands for. To a patient enrolled in the trial, they understand completely what that meant. And, again, it was an attempt to make that distinction between just run-of-the-mill junk mail to something that actually mattered.

MS. DUBLER: And what about phone calls and e-mails, aren't they guarded?

DR. AVELAR: Yeah. So when we look at phone calls and e-mails, part of the success that we've had lies in the fact that we've really personalized it. So we walk that fine line.

I understand your point about it'd be nice to have people share concepts and personal experiences. But they do want to do that, but they'd like to do it in a confidential way. So that's a challenge. So what we've done is we've really personalized things for them. So the phone calls, the web pages, when you actually arrive at the web page, it has been personalized.

And it takes into accommodation a bunch of personal preferences. So for instance, we actually ask, what is your preferred mode? How do you want to be contacted, by phone, by e-mail? And so a variety of those touches are aimed to customize it and to address the mediums that those patients really want to communicate through.

DR. LoCICERO: Dr. Leitch.

DR. LEITCH: Marilyn Leitch.

I think this is for Mentor, but it was mentioned that -- of people identified to have rupture on MRI, I think the number was only 29 percent that had implant removal at one year. And I was wondering what the -- if you had done any specific focused follow-up of those patients with a known rupture who didn't have removal and what their experiences were.

DR. WIXTROM: Okay, one of the elements of the study protocols is that, for the patients in whom rupture is identified, whether or not they have the device removed, those patients are followed to see if there's any difference in terms of complications or adverse health outcomes, and that's something that's tracked and reported, and we don't see any difference in that.

Now, it does go up a little bit over time. So the number that I quoted in the presentation was, if you look at patients who have an MRI and it identifies suspected rupture, if you go one year beyond that, using Kaplan-Meier estimates, it was 29 percent that had their devices removed. If you go

on to two years past there, it's 40, in the low 40s. But then, you know, if you're two years out, it may be for other reasons as well.

DR. LEITCH: So you're saying you did not identify any differences in effects of having the rupture?

DR. WIXTROM: And that's actually consistent. One of the Danish studies actually looked at untreated rupture and they looked at -- they screened patients with MRI, and there was a set of patients who had rupture identified, and what they did is they came back, then, and looked two years later, they did MRI again, and they also looked for various health endpoints as well, and again did not see that the rupture was producing adverse health effects.

DR. LoCICERO: Dr. Connor.

DR. CONNOR: So a question to either group. So, you know, I understand one reason for high loss to follow-up is a patient gets this and things are going well and so she, you know, feels no need to be in touch.

So let's say at, you know, year eight she has a host of symptoms, that autoimmune disease, who knows what. How easy is it for her to get back in touch with you? This is a naive question. Does she do know what type of implant she has? Does she know who to contact? Is she supposed to get in touch with her plastic surgeon, who may have moved the practice or isn't practicing, or is something like that? Or should she be getting in touch with the company, and does she know who to contact?

So, you know, if we don't hear from people who don't have events, that's not as big a deal. But if a patient is having events, we want to hear about, you know, eight years down the road, after she's been out of touch, I want to understand how easy it is for her to find you to report that, because we've seen from the letters we're getting, you know, we hear in our letters from women who have had events, you know, and who feel passionately about this. So if a women is then in that situation, how easy is it for her to report these things?

DR. AVELAR: So this is Allergan.

There's a bit of a difference ,and it depends if you're in the core pivotal study or if you're in a postapproval study like BIFS. In a situation like the core study, where these were all patients who started with a very rigorous study -- this is an IDE application -- it's much easier. Those patients don't forget that they were in a trial.

A little bit more of a challenge is when you get into a postapproval scenario. The scenario I think you're painting is the BIF patients who enrolled forgot they were enrolled. Eight years later they run into trouble; there is a mechanism. And what we do is those patients ultimately go and see a caregiver, a surgeon, most typically, and then that's addressed.

There's a feedback mechanism to the company. For instance, ruptures have a warranty policy, and usually that makes it back to product support. Within the company, product support then will reconcile any names

that come in and search the database to see if these patients had been involved in a study or not. And if they are, then it gets triggered in.

DR. CONNOR: Okay. So there's something, maybe, you know, a professional society of plastic surgeons, to tell someone, even if you get a patient that you didn't implant, to try to, you know, let us know exactly who that is. And you need to know them by name, presumably, to see if they were part of the BIF study.

DR. AVELAR: If it goes to another physician, it's a little bit more difficult. Obviously when it comes back, we try to track patient records and identify if they're involved in studies or not.

DR. CONNOR: Right, because that's what I'm wondering. If someone ends up, you know, at a rheumatologist or something like that, that wasn't their plastic surgeon, you know, how that feedback loop happens, because then it would seem like they would have to seek you out, rather than that rheumatologist or that other physician inform you.

DR. SPEAR: Scott Spear for Allergan.

I think this goes to that feedback loop at some point. It's handled by different processes. So I mean, in the follow-up study, sure, those patients are going to -- they know. And if it's a device-related thing, specifically that people can put two and two together, there's a warranty program. So patients would be pretty wise to, you know, take advantage of that. There's a big financial incentive for that.

If you're talking about some other disease that happens to somebody, someone has to put two and two together, and that almost falls into the medical care system and what Roger Wixtrom talked about, about how those cases are picked up and initially reported as case reports, et cetera.

But for any given patient to get back to Allergan that they had, you know, pericarditis and for Allergan to, you know, get that report, it's not going to come directly to Allergan, I don't think.

DR. LoCICERO: Does Mentor want to --

DR. AVELAR: Sorry. I'll just add to, you know, the other mechanism. I described a mechanism where it comes through the healthcare system. But this is also why the postapproval methodology is really important. We have MDR reporting, and that's another way that things get communicated to us. It could be through a hospital, it could be through a patient, it could be through a rheumatologist. But that MAUDE database becomes important.

As those patients come through, we have about 30 days to process. And, again, that's another mechanism where we look at the patients we have on file and who's in a trial and who's not.

DR. CANADY: John Canady for Mentor.

So with respect to the large PAS study, I mean, there's a prospective, proactive, ongoing attempt on our part to continue to contact

the patients. I mean they receive, you know, an inquiry at least on a yearly basis. So they should, you know, have the ability to reconnect.

DR. CONNOR: Yeah. And my concern is I assume they're more transient, though, if it's women, especially for augmentation. In their 20s and 30s, they're, you know, a transient population who, you know, if you keep sending things out every year, they, you know, are moving apartments or getting married and moving.

DR. CANADY: It is a very mobile population, that's true.

DR. LoCICERO: Dr. Glassman.

DR. GLASSMAN: Len Glassman.

Just a comment rather than a question for the Panel. We're talking about implant rupture as if it is a single event and a single type of happening, and that's not true.

For those people on the Panel who are not plastic surgeons or radiologists, I mean, implant ruptures are generally categorized as intracapsular and extra-capsular. You have the implant shell, which is the polymer outside lining of the implant, and then you have the fibrous capsule, which is the body's response. So there are two walls separating the silicone gel from the patient, basically.

And with an intracapsular rupture, where the polymer has ruptured but the fibrous capsule has not, most of those patients have no idea, if they don't get an MR, that they have a rupture. There is nothing

about their breast that's different, there's nothing about the shape or the way it feels. They are less likely, if they find out that it's ruptured, to do anything about it now that they know that there's no connective tissue disease issue, or at least they've been told that.

On the other hand, with an extra-capsular rupture, where the polymer is ruptured and the fibrous shell is ruptured, then you start to get into my breast has changed shape, I have these hard nodules, I have other symptoms or signs, and they're more likely to want to do something about it.

So when we listen to the statistics on rupture and reoperation, we need to keep in mind that we don't have the deep data to look at and say, oh, of course only 29 percent of people got re-operated, but they're all the ones that had extra-capsular rupture, maybe. So we just need to keep that in mind as we look at the data and talk about it later today. Thanks.

DR. LoCICERO: Dr. Galandiuk.

DR. GALANDIUK: I had a question for both sponsors, in terms of what they're doing to improve the informed consent process beyond just using booklets, because the booklets that patients probably aren't using that much or probably aren't reading that much are really not that effective.

DR. AVELAR: Allergan.

In terms of informed consent and booklets, what we're doing is we're trying to update them with news as it comes out with the data, as it evolves. The initial booklet had three-year data. The next booklet had seven-

year data. And now, with the submission that we have just put in this week, we're going to up-label for 10 years.

In terms of the content, one of the conditions of approval was to discuss with patients and look at recommendations that they had for booklets. We took a lot of their thoughts, a lot of their opinions, a lot of their ideas, and tried to incorporate them. But ultimately we have to vet those through the FDA, and some of those things were okayed, and some of those things, we were asked not to put them in.

DR. HONEIN: So I had a question for both sponsors. It seems like having two different PAS study designs and approaches is a real missed opportunity for being able to put the data together and perhaps look at rare outcomes. And I was wondering what the specific concerns might've been from the company perspective about using a standard design for this type of work.

DR. WIXTROM: You raise an excellent point. Actually there were a number of discussions at the time actually preceding the approval in November 2006. There was certainly interest of plastic surgeons, I think, FDA and manufacturers, and the potential benefit of having a single protocol. Actually, in terms of lessons learned, one of the questions before flaws, I think, in retrospect, if it had been done as a unified protocol, we would have better overall, even for both studies, in that. So I would say that would be an excellent approach going forward. Because, really, if one looks at the

endpoints, it's an identical -- essentially an identical set of objectives that FDA laid out for both manufacturers.

DR. AVELAR: Allergan. We agree. And that's, in fact, probably the number one point that I made when we looked at this retrospectively.

DR. LoCICERO: Dr. Jones.

DR. JONES: This afternoon we'll be talking about future study designs, and I'm wondering if I could ask both companies now to comment on that. What would be needed, in your opinion, to really accomplish really large studies like this?

I got the idea from the gentleman from Mentor that they're advocating going back to a really sort of passive approach to surveillance and the mechanisms that are already in place, and I'm wondering if you could just put out there what would it take to have the company and in particular other kinds of collaborations with professional organizations, or whatever you think might be useful. What would it take to accomplish a large study like this?

DR. WIXTROM: Well, I'd say, in terms of the postmarket setting that was described, the premarket studies, both the core and core continued access, you know, the recommendation that we made was to continue those out to 10 years to collect a number of the endpoints in that.

And, in fact, if we look -- if we take a specific example, at the current time, sort of the next iteration of the silicone breast implants are the form-stable implants that have been in use elsewhere in the world, and those

are working their way through the FDA regulatory review process at this time.

If we look at that in that situation, there's a core clinical trial. In that case, for Mentor, it's somewhere between 900 and 1,000 patients. And then there's the continued access study, which has 3,000 patients, if I remember right, right now. So if you followed those out to 10 years in the postmarket setting, that provides a pretty robust dataset.

And one of the things that I just mentioned briefly in my presentation because, as I understood, it's likely there will be a further presentation by one of the surgeons who helped implement this system, is there is a TOPS database which ASPS set up. It's HIPAA compliant. One of the really, I think, exciting new additions to that is that's incorporated the Breast-Q, which is a patient-reported outcomes measure that's been validated through the FDA guidance in that. And that's something, as I understand, that patients can tie directly in. So I think, going forward, if there was a sufficient participation in that type of effort, that's another source that might be available.

And then, as I mentioned in the presentation, I think, you know, the hope would be, from those new initiatives underway, there might be some measures there, too.

DR. LoCICERO: Dr. Hennessy.

DR. HENNESSY: Sean Hennessy.

This is a question for either sponsor. I'm wondering if you

could provide the number of devices that are implanted per year of both saline and silicone, and give a breakdown of what proportion of those are for reconstruction versus augmentation, and also talk about what the time trends are, what we can expect those numbers to look like in future years.

DR. AVELAR: This is Allergan.

Obviously, those are numbers that we'd be able to provide. We came here to talk about postapproval studies, but that's information we can certainly provide and we can bring that together.

DR. WIXTROM: You know, without the specific numbers, just to sort of generally address your question, in Europe, silicone gel implants represent probably 95 percent or more of implant usage. During the time of the moratorium, the primary implants available were the saline-filled implants, with the exception of patients who were in the adjunct trial or one of these core trials in that, too. Following the approval in November 2006, there's been a steady increase.

So I think the numbers I saw last generally were somewhere in the range of maybe 60 percent gel and 40 percent saline, and that trend seems to be continuing upward.

And I certainly agree with the comment made earlier this morning by FDA, that one can't directly compare the results of some of these different clinical trials. But some of the elements of the study design are quite similar, and if you look at the complication rates in prospective studies

from saline-filled implants versus the gel-filled implants -- and this was some data of earlier results were presented at the April 2005 Panel hearing -- the incidence rates for many of the complications are actually lower with the gel implants, and in some instances, statistically significantly lower. So that contributes to the thought as the trend will -- many believe will likely continue in the direction that's seen elsewhere in the world.

DR. HENNESSY: And do you have any sense for the number per year that are implanted and the mix of augmentation versus reconstruction?

DR. WIXTROM: I think FDA, in their presentation, had the numbers from ASPS on the number of augmentations. It's actually an ASPS statistic. We can certainly get that at break.

DR. HENNESSY: Thank you.

DR. LoCICERO: I think for follow-up purposes, we'd like to have that information by the time we start looking at the FDA's questions, and maybe both sponsors can provide that later.

One other thing that's come up is this issue of Kaplan-Meier curves, which I think a lot of us would like to have an opportunity to see. Can the FDA provide that, or if not, are the sponsors ready to provide that information?

DR. AVELAR: This is Allergan.

Again, we've compiled the 10-year data, so we can compile that information. We just need some time and we'll be happy to submit it to the

FDA.

DR. WIXTROM: With respect to the Kaplan-Meier analysis, which specific complications were you -- which particular graphs were you interested in seeing?

DR. LoCICERO: I think Dr. Connor was the one who brought that up first, so let's ask him what he'd like to see.

DR. CONNOR: Things like reoperation, the contracture one, because I think that's a big adverse event. I think, you know, the key adverse events.

DR. WIXTROM: The key complications.

DR. CONNOR: That way we can understand essentially when they're occurring, whether it's, you know, mainly up front or, you know, once you get through a few-month window or, you know, that sort of thing. So the key ones, including reoperation and explantation.

DR. WIXTROM: Right, we can get those together. And I certainly agree with you because, whenever I'm presenting on contracture, I find it much more informative to show the Kaplan-Meier curve, which, your point, you see more than 50 percent of capsular contracture that you're going to see out at eight years you've already seen by 12 to 18 months. And it tends to plateau much more for augmentation as compared to reconstruction. But, yeah, we can get those together.

DR. CONNOR: Is that for us? Because I think Dr. Avelar

mentioned turning it to FDA. I guess the question is, is that going to be done in a such a time frame that we can see it --

DR. WIXTROM: Yes, we have the slide. Yes.

DR. CONNOR: -- this afternoon or even, you know, tomorrow? Okay.

DR. WIXTROM: Yes, I have those with me.

DR. LoCICERO: Does the FDA care to comment? Dr. Krulewitch.

DR. KRULEWITCH: Within our reports, it's by time period, so we don't have the curves, so we'll defer to the companies to present those.

DR. LoCICERO: Okay. So we rely on both sponsors to provide that information hopefully by this afternoon, if they could, please.

Dr. Crouch.

MS. CROUCH: I think the gentleman from Mentor mentioned that, of the implants that were removed for rupture, 60 percent of them actually were determined not to have ruptured, and I wonder, if I have that correct, if you could comment on whether or not the rupture was supposedly diagnosed by MRI or by symptoms.

DR. WIXTROM: In that section of the presentation, actually, as mentioned, it was 63 to 64 percent of the devices that were returned that were found to have failed upon examination, the failure was attributable, when one evaluated the implants carefully, to sharp instrument damage.

And what was the second part of your question?

MS. CROUCH: I thought there were a number of the implants that you were examining that actually had determined not to have ruptured at all, though they were removed for the diagnosis of a rupture. So I was trying to understand whether or not the diagnosis was from an MRI or from symptoms or both.

DR. WIXTROM: Okay. Actually, as reflected in the device labeling, most ruptures are silent, and that's one of the primary reasons in the design of the core clinical trials why the MRI sub-study was implemented with the MRI evaluations at every two years. So in Mentor's core study, the vast majority of the ruptures were identified by MRI exam.

Now, with respect to evaluation of returned devices, the devices that are returned, some of them are returned as a result of suspected rupture. But there are also -- Mentor also gets devices that are removed. For instance, even in a size change operation, Mentor is interested in receiving those implants. So basically most implants that are taken out Mentor is interested in receiving.

So the short answer to your question is the vast majority of ruptures are identified by MRI, and that's the source of the returned implants. Although, as we heard from the data this morning, the majority of the patients who have a suspected rupture, by MRI, at least within a 12-month period, do not choose explant.

And I certainly concur with the comments that were made from

a radiologist's perspective in that, too. The vast majority, nearly all of the suspected or confirmed ruptures, were intracapsular. So that certainly does impact the decision of the patient and the surgeon.

DR. LoCICERO: Just a follow-up question to that. Not all devices that get explanted come out in one piece.

DR. WIXTROM: Correct.

DR. LoCICERO: And so I'm sure that you get a number of them that are damaged in one way or another. Can you tell the difference between a recent sharp injury and an old sharp injury?

DR. WIXTROM: That's an excellent question and that has been -- that's sort of been one of the dilemmas in evaluating some of this data over time, and that's why I think someone -- I forget who it was -- made a comment earlier this morning. Certainly if one has an MRI before the device is explanted, that certainly helps one interpret the data. In fact, in Mentor's core study, as I mentioned, most of the suspected ruptures were identified by MRI. So you have MRIs before the device was removed, and then if you remove the device and the only portion of that where you see a rent in the shell, you see the sharp instrument damage, well then that gives you a little bit better answer, a way of approaching that question.

But that certainly is an issue in evaluating these devices, is because oftentimes when these devices are being taken out, certainly the primary focus isn't on, you know, pristine handling of that implant coming

out. It's on, you know, the patient benefits.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: I'd like to ask both of the manufacturers just to explore a little bit further on this MRI issue. The MRIs have always kind of served a dual purpose and I think, in the original core study, one of the questions was, back in 2006, what is the incidence of silent rupture? So by getting the MRIs, this was an opportunity to determine the rate of rupture.

But at the same time, the MRIs are, for example, in the labeling that the FDA has on implants for patients, asking them to get MRIs so that they can direct what would be the proper course of action for them if the implant is ruptured.

So the MRIs have kind of played two different roles here, and since this cost is such an enormous burden on people who are paying this out of pocket, I think many of those patients are very puzzled about what is the right thing, aside from the study protocol in the core group.

So I guess, to the manufacturers, going forward, do you think that the 40,000 patients in each of the large studies should really need to continue to get these MRIs? And if so, what is the purpose of it? Is it only a therapeutic purpose, or are we still trying to get numbers on rates of rupture?

DR. AVELAR: So there are multiple parts of that, so let me try and handle that. I think, you know, the first thing is to remind us why we did

MRIs in the core study and why we did MRIs in the BIF study. So the MRIs in the core study was meant to try and address that very question, trying to understand sensitivity/specificity. Not only did we have the MRIs taken at the intervals that I had mentioned, but any time a patient was supposed to be explanted for whatever reason, an MRI was done beforehand.

That's in contrast to the BIF study. So in BIFS, the reason why patients -- I'm sorry. In BIFS, what we were looking for wasn't so much the MRI information but rather compliance with MRI. So we asked the question, are patients compliant with MRIs or not?

If we look at the ability to pick up ruptures, I think we've spoken to that, and the FDA spoke to that, also. A physical exam and a patient symptomatology will only probably pick up about 30 percent of silent ruptures, whereas MRIs will pick up about 89, 90 percent of silent ruptures. So it's certainly more accurate.

If we look at the BIF study and now ask the question, in the real world, how compliant are patients? I'd mentioned that it was less than five percent in general. And if we look at the different cohorts, you'll see 2.7, 3.1 percent, and probably the 3 percent number is what we're seeing right now, early on into the BIF study.

So in other words, if you ask a patient, here's your label, how compliant are you, you're seeing not very good compliance. And this really brings -- the question you're asking is, is there a different way to look at silent

rupture?

And I think there are a number of physicians, and I believe there's a bunch of radiologists who have been trying to champion that very same argument and suggest that perhaps ultrasound is an alternative that we should look at. I think there's a degree of comfort for the patients when they think about ultrasound versus MRI. Most patients don't have -- it's not right, it's not wrong, but most patients have a better understanding of what an ultrasound is. It's related to fetus. It's related to prenatal care. It seems to be more benign.

One of the issues with ultrasound that we've all experienced at one point or another is it can be very dependent -- the person rating it, the person using the transducer, the person using the machine, can be an enormous variable. MRIs, you know, have progressed, but so have ultrasound. And now with the advent of high-resolution ultrasound, I know that there's a body, and I've looked at the data from Bennington, who basically says we're getting pretty good with high-resolution ultrasound, and perhaps we should be looking at that.

DR. WIXTROM: Yeah, and I think Mentor shares most of the views that you just heard. Certainly in the core study, those MRIs were paid for and the intent was to get an idea of the silent rupture rate over time. The primary purpose in the past then was to look at compliance.

I think, though, it's actually maybe a little bit too early to really

draw many conclusions in terms of compliance from the large PAS trials because if you think for a moment about the fact that the FDA recommendations call patients to initiate MRI screening at three years and then every two years thereafter, Mentor's is just now at the three-year point, and I think we heard Allergan's is at a two-year point. So I think once patients get further past that point, I think we'll have a better feel for that.

And I would certainly echo the sentiments in terms of there's, you know, some very active investigation by different individuals, in terms of attempts to develop alternative methods for screening rupture, methods that might be done in a surgeon's office and methods that would be much less costly. And so there's really a hope, and there's certainly an effort underway to try and develop alternatives to address that issue.

DR. McGRATH: Thank you. I think those are responsive answers. I think it raises the question -- I mean, at the time that the FDA used that recommendation for labeling, that was the best advice available, you know, at three years and then every two years.

But I think one thing we really need to look at is that piece as well as your recommendations in your large -- each of your large studies, about whether that really is the best thing going forward, or can the MRIs be better targeted to patients who are having symptoms and therefore -- or have some physical change in there, around the implant area and perhaps not use this for undirected screening quite so frequently and broadly.

DR. LoCICERO: Dr. Mount.

DR. MOUNT: Del Mount.

This is a follow-up question to Dr. McGrath's. Regarding the core studies, you know, obviously you can't design a study to give you every answer, but sometimes you get answers that you weren't expecting to get from a study.

And the question I have is, have any of the MRIs and that study data have been helpful in identifying particular lots of, you know, implant numbers or, for proprietary sort of purposes, showing that maybe there's a certain lot number that have seemed to rupture more than others? And has that data not only come forward, but has it also helped you in guidance as far as product design, or even given you advice as far as recall of the lot that, you know, may not be as strong as the others?

DR. CANADY: Thank you. John Canady for Mentor.

No, it hasn't given us any information on any specific lots, and the MRIs have not resulted in any identifying information like that. But it's a good thought.

DR. CONNOR: I mean, is that because you haven't looked or you have looked and it's not there?

DR. WIXTROM: No, we've looked. It's a routine part of the product evaluation process, actually for more than just rupture, to look. When devices are returned, they're evaluated and then see, you know, is that

looking actually sometimes back at the records for development of that and then certainly seeing if there's any patterns that emerge. But that hasn't -- nothing like that has shown up with the ruptures.

DR. MOUNT: So, in essence, the MRI data have not really helped as far as product design or any sort of useful information except for rates of eventual decline of the implant or wear or tear?

DR. WIXTROM: Right. I think, in the core study, the MRIs sort of have achieved really the primary objective, and that was to really get a handle on the rate of silent rupture over time, so that patients and surgeons could be given accurate information in labeling on what that experience would be in the 0 to 10-year time tracking period.

I think it's interesting because if we go back and look at some of the information that was presented at the April 2005 panel hearing, we had information from an MRI study that was done over in the UK, and what they did is they brought in patients who had Mentor silicone gel implants for as long as 13 years, and they did MRIs. They had two independent readers evaluate those, explanted the devices to confirm whether rupture was present or not. And so there was a curve generated for the occurrence of rupture over time.

And I think, in what we're seeing in the core study, the results are tracking that. And we really don't see -- and we see, again at three years, as we presented, you really aren't seeing any -- much in the way of rupture at

that point. It's a later one.

DR. LoCICERO: Dr. Leitch.

DR. LEITCH: So it seems that there's some dissonance between the labeling and practice. I think one thing was said by Mentor, that it's not standard of practice to follow a patient with implants past one year. But yet the labeling is telling the patient to have an imaging study at a certain interval of time, which there's kind of nobody to order that for her. I mean, it wouldn't be something her primary care doctor would likely know or think about to do. So it would sound like that that responsibility would then fall to the plastic surgeon as the one to "order that test."

And then if the labeling says the implant should be removed if there's rupture, but the rupture is silent and asymptomatic and the patient has no complaints, what are you supposed to do with that recommendation?

I don't know if the sponsors want to respond to that, but I think we probably have to respond to that issue because you have sort of a disconnect between those practices and recommendations.

DR. AVELAR: So Allergan.

I'll reply to that in two forms. As a sponsor, we have to follow the label, we have to endorse the label. If we veer from that, it's an off-label recommendation. But your question is also trying to figure out what are surgeons doing in practice. So I'm going to ask Dr. Scott Spear.

DR. SPEAR: Thanks. I think what Dr. Wixtrom was talking about

is what happens often in the real world versus what is recommended. So I think most of the plastic surgery societies, and speaking as myself as an individual surgeon, recommend that patients have ongoing lifetime follow-up with their surgeons after an implantable device, including a breast implant.

I think what Dr. Wixtrom was pointing to is that a lot of patients don't comply with that outside the studies, and I think that's one of the things that we would encourage in the labeling, and in terms of the plastic surgery societies, that patients with implantable devices see their physicians at intervals every two or three years to make sure that they aren't having any symptoms that they haven't attributed to the device.

DR. CANADY: I think, though, that raises a very good point. It is confusing. It's confusing for patients and it's confusing for physicians, and as we've already covered, it's a very mobile patient population. So, you know, I'd hope as we work through this going forward, I agree with everything that's been said, but I think that those are issues that need to be brought into alignment so that patients aren't confused about what they, you know, actually should be doing.

DR. LoCICERO: Yes.

MS. MATTIVI: Kris Mattivi, the Consumer Representative, again.

So along those same lines, in terms of this is often a young population but an electronically very savvy population, in terms of, again,

long-term engagement on the part of the patient population, do the patients get that from like the BIFS website? Do they get that information if a patient doesn't participate in their annual survey for two or three or five years but they're part of this long-term study? Do they continue to get contacted by the sponsor? Are they encouraged to share that information?

And then a second part to that. Has there been any thought to the use of electronic medical record, electronic health record, in terms of long-term follow-up?

MS. MONROE: Rose Monroe, Allergan.

Yes, the outreach to the participant continues. We don't consider the participants lost to follow-up until the end of the study. So for BIFS it's still very early on for that large PAS. But we will continue to reach out to the participant until she finishes her annual questionnaire.

So whether we're using all mediums, as I mentioned earlier, in the mail, IVRS, a live phone call, e-mails, and we start that outreach six months before the annual questionnaire is due when their window opens, and it's going to continue almost right -- it's going to back up right up to their next window until they complete their annual questionnaire, and it's going to start all over again.

Okay, you know what? You missed your year one annual questionnaire, but guess what? Here's another opportunity. You're now in your year two window. It's time to complete your annual questionnaire. And

that outreach starts again.

And of course we have other -- if we believe that we don't have accurate contact information, we are constantly looking at search engines like LexisNexis, just going even to the web, looking at NDI death searches, I mean. So we're using all of those mediums to try and get good contact information for the participants.

One of the mailings that we send out to the participants includes a contact information change card. So on an annual basis they have this little postage-paid card that they can send to us at any time during their participation and say, hey, I've moved. I get particular joy when I have a patient call up and say hey, I'm in your BIFS program; I've moved and I wanted to let you know. It tells me it's top of mind for them.

MS. SELLEY: And for Mentor, we do very similar tracking. We continue to follow the patients, contact them, and until they let us know that they want to be discontinued from the study, we continue to track them and we use various systems in order to do that.

DR. HONEIN: So what are the levels of sort of refusals or requests to be discontinued and no longer contacted versus people that just haven't been in full compliance and followed up?

MS. SELLEY: About .8 percent notification from patients to be discontinued.

DR. LoCICERO: Just for clarification, that was less than one

percent? .8 percent?

MS. SELLEY: Yes, that's correct.

MS. MONROE: Rose Monroe.

The discontinuation rate for the BIFS is currently 1.5 percent.

DR. LoCICERO: Ms. Dubler.

DR. WIXTROM: And actually we have the answer to one of the earlier questions that was asked, in terms of the number of devices used -- the numbers from the society, one of the officers came forward. If you look at the last two years, about 300,000 breast augmentations, about 85,000 breast reconstruction, and it's a two-to-one ratio of silicone gel to saline.

DR. LoCICERO: Ms. Dubler.

MS. DUBLER: Nancy Dubler.

My question, I'm sure, reflects my confusion. But what I don't -- here are these women enrolled in various studies, but they are only a fraction or a part of the total number of women who receive breast implants. What would it take to move from these studies to a more generalizable registry? And has that been considered? And who would be responsible for doing that? And is it a good or a bad idea?

DR. WIXTROM: I think there's different opportunities depending on which cohorts you're thinking about. With respect to breast reconstruction patients, since that initial procedure is covered by insurance, then one has a much better opportunity then to track them in, for instance,

the administrative health databases.

And really, though, we didn't really address it that much in the presentation, I think, over the long term, not just for breast implants but for a lot of medical devices, that makes a lot of sense for the rare health conditions because it doesn't require any follow-up of the patient back to the original surgeon or getting the information back directly to the manufacturer.

The real challenge -- there have been a lot of discussions in terms of how to potentially overcome that issue -- is with the augmentation patients. Certainly both in the U.S. and Canada they fill out device tracking forms at the time of surgery, and that information is provided back to the manufacturers.

But the legislative purpose for that, both in the U.S. and in Canada, is to notify the patients in the event that there's any adverse situations they need to be informed of. Alternatively, you know, if the laws were different, that might provide a way to track them in such databases, but that's not where things are right now.

But certainly in terms of addressing one of the major challenges of follow-up, the types of approaches that you're suggesting, I think, are ideal if one can overcome some of those hurdles.

DR. LoCICERO: Dr. Galandiuk. As she's getting ready to ask her question, the morning is winding down, so each of you get ready for your final question before we stop for the morning.

DR. GALANDIUK: Yeah, I'm Susan Galandiuk.

Like Ms. Dubler, I also have a concern about all of the women who aren't participating in these follow-up studies. And it's interesting if you look at both companies' websites. While safety information is there, it's fairly difficult to negotiate your way to find the PDF files that list this. I wonder if it wouldn't be in the interest of the patients to have this in a much more easily identifiable area, more on the home page where it's easy to link to, and if it wouldn't be an easy thing to also have an adverse reporting thing somehow linked to these websites for patients who aren't in these trials.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: I just wanted to get back to the registry thing because I just need a clarification from the manufacturers. But it's my understanding that a registry is not a study. In other words, a registry just gives you the name of the person and lets the person know they're in it, and then it would be, as you said, for purposes of recall, but you wouldn't be gathering any data about the devices during the course that they're in this registry. Am I correct about that?

DR. WIXTROM: What we were talking about was, I guess, a concept moving forward. So what has been discussed as an idea at this point is like, for instance, let's take breast reconstruction patients. If you are able to identify a unique identifier for them at the time of surgery, because that's reimbursed through insurance, then if one's concern, for instance, is

following rare conditions like cancer or connective tissue disease in that population over time, then there are studies -- in fact, there have been several of these done in Canada -- where they have tracked the occurrence of connective tissue disease, not for breast implants, but just overall, using administrative health databases and combinations of them that were much more effective.

So that is actually using it not just in a passive way, but using the -- once one has the identification of the patients with implants, to then go to those databases and see, well, if we look out over time, what do we see? And, in fact, that's the approach that's been taken with some of the Scandinavian registries that we have, in particular the Danish registry for plastic surgery of the breast, which has contributed, I think, some very valuable information and literature.

The challenge in the United States certainly is, as was mentioned in one of the earlier discussions, women with breast implants in the U.S., it tends to be a more mobile population. And the current situation in the U.S. is also that people change insurance companies. So if one's relying on insurance databases, you know, there's that issue. Other places where they have single-payer healthcare systems, less of an issue.

DR. POGGIO: Let me add to that. Gene Poggio again.

I think the term registry gets used different ways. Sometimes it's exactly as you mentioned, just the very limited data, a device tracking

system that you get. You know, the patient's name is in there, maybe contact information and so forth, and that's the end of it.

There are other kinds of registries. There are many registries that are either product specific or disease specific that are -- an epidemiologist would call them a current cohort study, where there'd be a set of patients identified, enrolled, and with built-in follow-up into the system. It could be follow-up based on visits, almost like a trial, or it could be a survey follow-up and so forth. But the whole intent is to follow those patients forward in time with active data collection.

So the term gets used both ways, and I think probably it's the latter. When the FDA raised the issue of possibly patient registries, especially if we were designing a new registry as a way to do -- as a postmarket study, I think it would be this latter kind of registry that one has in mind.

DR. AVELAR: I just want to make one final comment about registries. Conceptually, it makes a lot of sense. Conceptually, pooling the data, it makes a lot of sense.

I do want to make one obvious point. You're looking at two sponsors here who have a great deal of experience right now with their devices, and the only cautionary word I would say is sometimes creating a lump and trying to put everything into the same category of a breast implant.

So if we look at our manufacturing process, and I'm sure if you speak to Mentor, they'll speak, you know, very eloquently to their

manufacturing processes, leachables, extractables, all of the little things that can actually have impact.

If we look at what we've learned from things like drug-eluting stents where we tried to create registries and at one point there was a thought, well, all drug-eluting stents are the same and what can we learn? It's true to a certain extent. But later on, as we started looking at the different components of the different manufacturers, we saw very different things coming from different ones.

So a registry is a great idea, but trying to making sure that we understand those who are coming in with datasets and those who are not, and what do we know and how do we pool them and when do we separate them?

DR. LoCICERO: Any last burning questions this morning?

MS. DUBLER: I actually have a brief comment, not a question, both for the sponsors, who have been so gracious to come and really give very helpful answers, and to the FDA, who works with them on these brochures and informed consent.

And this has been a singular interest of mine, that the notion of informed consent in medicine, in research, has been -- its effectiveness has largely been recognized as very limited by some very good epidemiological studies and epistemological studies over the years. I think that the notion of informed consent in breast augmentation, not in reconstruction, is an even

more endangered species because, in general, people come to a physician when they have a problem, and I know that the women who come for augmentation perceive that they have a problem.

But indeed the level of advertising in the breast augmentation area was, the last time I looked at it, pretty ferocious, and the same level of advertising doesn't exist in many other areas of medicine. And so we're in general, in the informed consent process, you want to give an even-handed treatment of risks and benefits.

Here, where a woman comes quite convinced of the benefit, I'm not sure that it isn't morally mandatory to give a much more detailed explanation of risks.

So the balance in the usual informed consent dialogue or process, which is usually distilled down to a form, has even less power in the area in which we're working. And I think at least that is my perception that I'd like to add to the mix. Thank you.

DR. LoCICERO: Thanks. Dr. Whorton.

DR. WHORTON: Just one comment, and it goes back to what Dr. McGrath commented on earlier, having to do with the MRI. I read about the issues.

If there were signs, symptoms, and complications that may be presented by an implant patient maybe 8, 9, 10 years after implant, as they become manifest, to what extent would those be either missed or not tallied

in the complication rates without MRI? What would be missed in the diagnosis of complications in people without MRI, and what would that have as an implication for a postmarketing study?

DR. SPEAR: This is Scott Spear speaking for Allergan.

As I understand the question, I think the only complication that would be missed would be silent rupture. I don't think those patients turn out to have other things going on except for silent rupture.

I do want to emphasize, since I don't think it's been mentioned this morning, that MRI does -- it's not 100 percent accurate, and it has false positives. And so until those devices come out, you don't know for sure if those patients actually have a rupture, even though both companies count them as ruptures based upon the MRIs. So if anything, I think it overrates the rupture rate.

Does that answer your question?

DR. WHORTON: If they have complications and did have an MRI, it may be a false positive. But nevertheless, it does indicate the presence of a rupture.

DR. SPEAR: Yeah, I think it picks up patients who are asymptomatic because, if they were symptomatic, they would often have an intervention for some other reason. It would get an MRI, at least in the Allergan protocol. If they're going to have a device removed, they get an MRI prior to removal.

DR. WHORTON: But would the presence of signs and symptoms suggest that they should have the MRI to demonstrate that there was or was not a rupture?

DR. SPEAR: It would be case-by-case if there was some reason why you needed the MRI to look at the device. But regardless of why the device is going to be removed, they would get an MRI as part of the protocol for removal. For example, if the patient had capsular contracture, you know, the MRI wouldn't pick that up, that'd be a clinical finding, but they would get an MRI anyway. But it probably doesn't contribute particularly to the findings.

DR. LoCICERO: Okay, we'll now break for lunch. Panel members, please do not discuss the meeting topic during lunch amongst yourselves or with any member of the audience. We will reconvene in this room in approximately one hour, at 1:00 p.m., where we have a very aggressive afternoon. Please take any personal belongings you want with you at this time. The room will be secured by the FDA staff during the lunch break. You will not be allowed back in the room until we reconvene. Thank you.

(Whereupon, at 12:00 p.m. a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:05 p.m.)

DR. LoCICERO: It's now a little after 1:00. I would like to resume this Panel. We will now proceed to the Open Public Hearing portion of the meeting.

Public attendees are given the opportunity to address the Panel and present data, information, or views relevant to the meeting agenda. In just a moment, Mr. Swink is going to read the disclosure process statement.

As a preliminary, we have a very large number of open public speakers. We have well over 30 for today, and we're going to go through the procedure in some detail. We appreciate it if you would stick with your schedule.

MR. SWINK: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the Open Public Hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationships that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's

payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. LoCICERO: I'm going to go over the process, which will hopefully ensure a smooth transition from one speaker to the next.

Please be ahead of your schedule, if you can, and be prepared to get up as soon as we're ready to call your name. You will have five minutes for your remarks. When you begin to speak, a green light will appear. A yellow light will appear with one minute remaining. At the end of the five minutes a red light will appear and your microphone will be turned off. If you finish before five minutes and the light is still green, do not feel like you have to continue speaking.

(Laughter.)

DR. LoCICERO: We would very much appreciate banking those minutes as we move along.

Speakers are going to be grouped together, and after somewhere between 5 and 10, we will stop and have questions from the Panel to that group of speakers. If recognized by the Chair, please approach the podium and answer the questions for us.

The Panel is interested in your comments and wishes to fully

understand the context of your comments. For those of you reporting a case history of adverse events, please state whether the individual in the case history was a participant in the postapproval studies we're talking about during this panel meeting, of either sponsor, or whether that individual reported the adverse event to the FDA through the MedWatch program. This will help us to frame those case histories.

I would like to remind the public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the request of the Panel Chair.

Please remember that the topic of this meeting is the future of postapproval studies for silicone gel-filled breast implants. We encourage you, the open public speaker, to stay in the realm of this topic.

Our first speaker is going to be Diana Zuckerman. Dr. Zuckerman, please come to the microphone. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting.

DR. ZUCKERMAN: I'm Dr. Diana Zuckerman. I'm president of the National Research Center for Women and Families. Our center does not accept money from medical device companies, so the center has no conflicts of interest. I have stock in Johnson & Johnson, and Mentor is a subsidiary of Johnson & Johnson, but I will not be saying anything nice about Mentor today.

My perspective is as someone trained in epidemiology at Yale Medical School. I was on the faculty at Vassar and Yale, conducted research at Harvard, and have been in the Washington area doing health policy research and advocacy for the last 20-plus years. I am also a fellow at the Center for Bioethics at the University of Pennsylvania.

I'm going to talk a little about the data. First, I don't think I have to go over this too much. You already know what the response rate was, the very high loss to follow-up in the large study, in the adjunct study, as you see on these slides, and also in the core study. So in none of these studies do we have a really good representative sample, although the short-term data in the large study for reconstruction patients is certainly better.

I want to talk about the rupture rate because it's quite misleading. The companies like to talk about rupture rate as a rate of rupture per implant, but in the past, they've also talked about per patient. And if you look at this slide, you will see that the per-patient rate is almost twice as high as the per-implant rate.

So when you look at the data in the materials that you were given by the FDA and that the FDA has on their website, please keep in mind that it's per implant.

But if you look in these earlier data from three years and so on, you can see in the yellow numbers that the per-patient rupture rate is actually almost twice as high, and you can see that both for Allergan and

Mentor.

So why is the follow-up so poor? Obviously Mentor did not do as good a job as Allergan, yet they have the same kind of patients. Why is it that they did such a poor job in the large study?

We also need to remember that because plastic surgeons have talked a lot to their patients about how safe implants are, that gives patients a little less incentive to come back for follow-up; because they're under the impression that implants are so safe, therefore, these studies aren't that important.

And we've also heard from many patients. Our center hears from thousands of implant patients, I'm sorry to say, who've had problems, and they talk about being fired by their plastic surgeons; that when women come back with multiple problems with their implants, they're not as welcome after the first time. So they lose their relationship with their plastic surgeon and they're no longer going back, and that's part of the reason why they're dropping out. But you'll hear more about that directly from patients.

I just wanted to look at these cumulative complications. You can see they do get very high, especially reoperations and removals. Remember that, to get an implant removed, the women have to pay for it, and one of the reasons why the removal rate isn't higher is because so many women cannot afford the $6,000 or $10,000, or whatever amount of dollars that it costs to get implants taken out. It is not usually covered by insurance

unless they're reconstruction patients. And the women in studies sometimes could not get insurance to cover it because they were in a study. And you'll hear about that from some of the patients.

So I looked at complications separately, looked at it for Allergan and for Mentor. I wanted you to see that in some cases the cumulative rate of complications is actually going down in 10 years. Now, that should not happen because it's cumulative. So the rate should be higher at 10 years than it is at 3 years. But as you can see, swelling, the cumulative rate went down from 23 percent to 9 percent for Allergan, and that's not the only place.

Several other places, Mentor in particular, for the cosmetic complications, for augmentation patients, hypertrophic scarring and ptosis, which is sagging, isn't even reported at eight years. And yet you know that sagging is more of a problem eight years later than it is two years later. So there's something fishy about some of these numbers. They're missing or they're getting lower.

And I don't have time to go through all of these numbers, but I did want to show you, here are some more from Mentor, where, again, you have extrusion and necrosis, which had numbers at these lower years, two years and three years, according to FDA statistics, but nothing at eight years. And then, when you look at cosmetic complications for Mentor, they're totally missing for asymmetry, ptosis -- this is reconstruction -- scarring and wrinkling. So you have more than you did.

In conclusion, incentives are lacking for the companies and the surgeons, the data aren't capturing the kind of problems that women are telling us they're having, and remember that the research literature has primarily been funded by implant companies and medical foundations that have conflicts of interest on this topic. So that's why we need independent research by the FDA.

Thank you very much. And I'll be glad to answer any questions.

DR. LoCICERO: Thank you. Our next presentation is a collection. It's going to be presented on behalf of the following individuals: Kathy Nye, Pam Saraceni, and Anne Stansell.

MS. de BRAVO: Hi, I'm Brendel France de Bravo, and I'm reading for women who couldn't make it today.

"My name is Kathleen VanFossen Nye, from Reading, Pennsylvania. I'm not well enough to travel to this meeting, so I thank you for listening to my words.

"I first got breast implants after undergoing a bilateral mastectomy at 22. My experience is like a history book on breast implants because I started with some of the early implants, and those were repeatedly replaced as newer models became available.

"I beseech you to make sure that well-designed and implemented long-term studies are conducted on all breast implants that are sold. Then make these studies available to the public on the internet so

women can read them for full disclosure.

"When I was 22, the doctor claimed I was lucky to live when reconstruction was available with silicone breast implants. He said, before the implants, I would've walked around with a sunken chest. He also said that they would never sag and that I would be the sexiest old lady in the nursing home. They would even self-seal if I was stabbed in the breast."

And we have photos here.

"I wasn't so lucky. My original breast implants had to be cut off my chest wall because the mesh backing from the implants grew into the chest wall. The implants had become as hard as rocks. I was told that the new silicone gel implants were greatly improved and would not get hard. If they did, all the doctor had to do was squeeze the breast until they broke the scar tissue capsule. These claims were not true.

"After five years of squeezing the hardened breast, I could no longer take the pain. My doctor told me it was my fault because I had no breast tissue. However, he told me that the new Meme implants were covered with polyurethane foam that would stay soft and never get hard. So he was going to use these new and improved implants.

"When asked about the safety of the foam, I was told to trust the doctor because he knew what was best for me. And yet the new implants also got hard. They were removed and I had surgery to get a new set of Meme implants.

"For three years, I was weak and sick and after visiting three doctors, complaining of pain and lumps on the edge of the implant, they told me it was scar tissue. One doctor said, to give me peace of mind, he would remove the lumps. The implants were removed and the three lumps were biopsied. Foreign material was found in two of the masses. The mass that was sandwiched between the other two was cancer. After chemo and radiation treatments, I was implanted once again against my wishes. Within three months, I developed necrosis and the implant pushed itself up and out through my skin.

"My physical health has suffered greatly. I have had over 25 breast-related surgeries, including six sets of implants and four single silicone implants, two expanders, and four individual saline for the left breast. I now have lupus and many other health problems.

"I've given my history to show you that there is always great optimism about the newly designed implants. But as the years go by, optimism gives way to reality, and those old implants are always replaced with new ones, until those new ones become the bad old implants that need to be replaced.

"It is 49 years and about three generations of women since the first breast implants. If the manufacturers make safety claims, they should back them up with studies that provide accurate long-term data, not biased samples where half the patients are missing and we don't know if the half

that are missing are healthy or terribly sick."

And this is from Pam Noonan-Saraceni coming up.

"I was diagnosed with breast cancer and had a mastectomy at the age of 25. I waited five years before I decided to have reconstructive surgery. I played tennis, jogged, and taught aerobics, but the prosthesis often shifted or fell out of my bra when I perspired. So as a well-educated women, I did my homework on breast implants prior to choosing the plastic surgery to perform my reconstructive surgery. However, I was told that they would last a lifetime and 'complications were rare.'

"Within three months of the initial reconstruction, I was back on the operating table. My body had formed a capsule around the implant, and the implant had shifted up and under my collarbone. The searing pain at that time was causing my shoulder to become immobile.

"My symptoms began slowly. At first I attributed the fatigue, aches, and pains to just getting older. I was only 36 years old. This was six years after I had been implanted. Then I got a severe case of the flu, and six weeks later I was still so fatigued that my life was being drastically affected. I had GI problems, sleep disorders, night sweats, chronic fatigue, myalgias, and joint pain.

"Before I had the implant removed -- this is 10 years after the initial reconstruction -- I was again wearing a partial prosthesis over the implant. Capsular contracture had again become a problem, and I was

misshapen and lopsided. The explantation was the fifth surgery at my breast site.

"I never fully recovered. I have gone to various doctors and specialists and have been given a list of various possible diagnoses. Atypical connective tissue disease is number one. But that diagnosis was made quite a bit later, not within the first 10 years.

"To date, my out-of-pocket medical expenses exceed $40,000. My husband and I are self-insured. The insurance policy that we took out carried an exclusion. I was not covered for any illness or disability related to the reconstructive surgery. Apparently, the insurance companies understood that there are health risks associated with breast implants and they are not willing to bear the financial costs.

"This is not a miracle cure for me, but I hope that by telling you what happened to me, you will understand why better research on breast implants is so important."

Thank you.

UNIDENTIFIED SPEAKER: "My name is Anne Stansell, and I live in New Mexico. I wish I could be here today, but I hope you will listen to my story.

"I am a breast cancer survivor. I was diagnosed at the age of 39. The doctor said I needed mastectomies, radiation therapy, and breast implants. Implants were just part of the treatment, no discussion. I trusted

the doctors who I felt had just saved my life. I was fine for the first five years. Then I became very ill. I was diagnosed with Grave's disease and fibromyalgia. My eyes were so dry that my retina tore. My implants were taken out about two years later. I had to fight with my insurance company to get them to cover the removal.

"Half of one of my implants was gone. Where did the silicone go? I don't know. Here's a photo of me with my half-empty implants. They couldn't remove all the silicone from my body, but even so, I began to get better almost immediately. My family noticed the difference even before I did. I'm still recovering and I can work some now.

"When I heard about the new postmarket studies, I saw that the complication rate was high, but was surprised that the complication rate wasn't even higher. I had many of the same local complications. I can't even remember how many surgeries I needed. Silicone was found in my side when it migrated from the broken implants.

"At a previous meeting, the data indicated that cancer patients and augmentation patients also had an increase in some autoimmune symptoms during the first two years after getting implants. I think that my symptoms started in the third year, so it's likely that the signs and symptoms will increase over time, just like mine did. But it doesn't seem that the postmarket studies measured symptoms. It seems like they just measured diagnosed diseases.

"When the FDA approved breast implants, they demanded postmarket studies to find out how often these debilitating complications occur. But based on the women I've talked to with breast implants, it seems that women with implant problems tend to stop going to their plastic surgeons and are therefore dropping out or being intentionally dropped out of the studies.

"I didn't have informed consent as a cancer patient, and from what I hear from other patients, that is still true today.

"This meeting is focused on research, but to do the right research, you need to listen to the patients who were harmed by implants. We illustrate the data. We are examples of what can and has happened to tens of thousands of women across the country."

This is from all three women.

"So far, the postmarket studies have all started studying women from the time they got implants, for the next 10 years, although many women dropped out of the studies before 10 years had passed. In our experience, many women with implant problems have told us that they no longer feel welcome at their plastic surgeon's office, so they have sought healthcare from other doctors. We are concerned that those are the women who dropped out of the postmarket studies. If they are, then the complication rate is much higher than the studies are reporting.

"We have heard on the news where plastic surgeons say that

breast implants have been studied more than any other medical device. We don't know if that's true, but if it is true, this is an indictment of research on other medical devices.

"The studies of breast implants aren't asking the right questions. You need independent researchers, not the implant companies, to do this research.

"We may not be typical breast cancer reconstruction patients, but we have talked to a lot of women who have stories just like ours. The FDA needs to interview women like us and ask questions about our kinds of symptoms, then include the symptoms in the studies that are done. And why not find the women who were in the implant studies that started 10 years ago and follow them for the next 10 years. Complications are much more rare at first and increase over time. So starting with women who had implants put in 10 years ago would provide much more useful safety information than starting with women who got implants two years ago."

Thank you.

DR. LoCICERO: Thank you. Our next speaker will be Linda MacDonald Glenn.

MS. MacDONALD GLENN: Hi, my name is Linda MacDonald Glenn, and I am testifying today on behalf of the Institute for Ethics and Emerging Technology, a nonprofit, nonpartisan public policy institute dedicated to ensuring that men's and women's voices, health and life

experiences, are brought to bear on ethical issues in healthcare and technology. My credentials are as a biomedical ethicist, attorney, legislative counsel, educator, and patient advocate. I have no financial conflicts of interest.

In 2006, when the FDA approved silicone breast implants, gel implants, it was with certain provisos. It required manufacturers to follow their preexisting study groups of silicone patients for 10 years and to create a database of 80,000 new patients, provisos that recognized long-term safety and informed consent as concerns. Unfortunately, many questions about long-term safety and informed consent will not be answered from this group because Mentor has lost track of 79 percent of the women in their so-called required 10-year study.

Informed consent of clinical treatments is one of the cornerstones of contemporary medical ethics. It is so much more than the patient's right to choose. If it were only about the right to choose, the FDA would not have the authority to regulate medical products. Informed consent is an ongoing process, not a piece of paper and certainly not a discrete moment in time. Merely giving information is too passive a process. And as our knowledge and our information changes, so must the process and the conversation.

The two-year studies the companies conducted for previous approval showed a significant increase in several autoimmune symptoms

such as joint pain and chronic fatigue, and those increases were maintained when age was statistically controlled. And since those data were analyzed for the FDA six years ago, two odd things have happened. First, those findings, which were in official documents on the FDA website, were not included in the patient booklets that the FDA requires companies to give to patients. And, second, it seems that those questions were not included in the longer-term follow-up of the core studies for the two companies.

So as this Committee considers what research is needed now, I have three recommendations. Number one, since the implants made by both companies were approved and contingent on postmarket studies, and since Mentor has completely failed to conduct those studies in a way that can provide useful safety information, I ask this Panel to advise the FDA to rescind approval for Mentor breast implants.

Number two, this Panel should recommend that Allergan be given an additional year to prove that they are taking these postmarket research requirements seriously. I do not believe that Allergan's online questionnaire is an appropriate way to gather accurate medical information about women with implants. There are so many other statistical ways, more accurate ways.

Number three, this Panel should recommend better-designed studies that Mentor and Allergan should pay for but not control or analyze. These studies should take a careful look at the psychological benefits, if any,

of breast implants. And they should also study the impact of breast implants on patients with a family history or personal history of autoimmune symptoms before they got breast implants, to see if those patients are more vulnerable to autoimmune reactions to the implants.

In terms of ethically sound decision-making, the path this Committee ought to take is clear. Breast implants should remain only on the market if companies abide by the postmarket requirements to provide data on long-term safety and efficacy. Mentor has not done so.

DR. LoCICERO: Please sum up.

MS. MacDONALD GLENN: And although it might still prove itself, their data-gathering methods are questionable.

Thank you for your thoughtful consideration and for listening today. I will be happy to take questions.

DR. LoCICERO: Next is Bettye Green.

DR. GITTERMAN: Thank you. I apologize, we've made a switch in the schedule. I'm a practicing pediatrician and have to go back to see patients, and we kindly did that. Thank you.

My name is Dr. Benjamin Gitterman. I'm a board-certified pediatrician and an expert in pediatric and adolescent health. Although I'm speaking as an individual, I have been a member of the American Academy of Pediatrics' executive committee on children's environmental health and until recently was the co-founder and co-director of the Pediatric Environmental

Health Specialty Unit in the Mid-Atlantic region, one of the 10 federally funded Pediatric Environmental Health Specialty Units organized by ATSDR. I'm a resident of the District and I practice and teach in both Washington, D.C., and Maryland. I have no conflicts of interest of financial relationships of any kind to this.

Better research is still needed on the long-term effect of breast implants. Speaking from my perspective as a pediatrician, research is especially lacking on the impact on teenagers who undergo breast augmentation, as is lacking as well on the possible impact of breast milk from women with implants.

The FDA approved silicone gel implants for women over 22 and saline implants for women over 18. However, it is legal for young women of any age to get either type of breast implant. In fact, even in the study submitted to the FDA by Mentor, there were 556 young women under 22 who had silicone gel breast implants, and under 22 was too young for the enrollment criteria and is an off-label use.

If plastic surgeons were as unconcerned about this in a study conducted for the FDA, despite this being an unapproved use that did not meet the study enrollment control, imagine how many young women under 22 are getting these implants in the real world.

These age criteria and restrictions are of particular concern because many, if not all, breast implants will eventually break or leak. If a

teen or a young women gets implants in her late teen years or even in her 20s, she's highly likely to need to have them removed and replaced at least four times during her lifetime. That would be every 15 years, which is longer than many implants last. And will she have the financial resources to replace the leaking implants on a timely basis before the silicone migrates to her lymph nodes?

Another consideration is will she be able to spend approximately $2,000 every other year just to undergo an MRI to check for leakage, as the FDA recommends, but frequently may not be covered by her health insurance, if she has it?

As a teenager or a young woman, is she able to make a mature informed decision about either the future health or financial risks of breast implants for her? Research indicates what most of us in this room already know logically, that many young women and men are usually unable to fully appreciate and make appropriate decisions about their risks in their future because they are not yet fully mature decision-makers.

In reviewing the well-meaning 45-page booklet that the FDA has approved for patients to warn them of the risks of either saline or silicone gel breast implants, I can say with confidence that it is much too long, technical, and complicated to provide true informed consent for teenagers.

We are strongly demonstrating that residue levels of many chemicals have been found in breast milk. Even if a very good laboratory

generates the test results, there are no accepted normal or safe values of these chemicals in breast milk which are known. Breastfeeding is recommended still over infant formula in almost all circumstances of chemical contamination residue in maternal breast milk. So we're certainly not going to tell a women who has implants to stop breastfeeding. Yet the long-term effects in children and infants are only minimally understood in the case of a few chemicals. While breast implants have been sold in the United States for more than 40 years, very few studies have been done on the impact of implants on breast milk and on breastfeeding.

The postmarket studies you're examining at this meeting attempt to evaluate the impact on breastfeeding and other reproductive measures. But the small number of pregnancies and the enormous loss to follow-up of the augmentation patients means that information cannot be conclusive or reliable.

Less than 20 percent of the Mentor augmentation patients and about 53 percent of the Allergan augmentation patients stayed in the study for the first two, three years; too few to make any generalization about any of the data and certainly insufficient to evaluate relatively infrequent outcomes such as pregnancy and breastfeeding. Yet the FDA says on their website, there is no evidence of reproductive problems. That may be true, but there is no evidence of safety either. The precautionary principle of exposure to potential toxicants has not been considered here, and there isn't

enough good scientific evidence to draw conclusions about safety or risk.

In conclusion, the implant companies are not doing an acceptable job of collecting the kind of long-term data needed to study the impact of breast implants on breastfeeding or reproduction. The FDA should not consider the available data even close to adequate in drawing conclusions about the safety of implants on breastfeeding or other reproductive issues. The Agency should be more proactive in reducing the number of women under 22 who are getting silicone implants off label and improving informed consent for women.

I apologize for my dry throat. Thank you very much.

DR. LoCICERO: Thank you. Are you going to stay for a few minutes?

DR. GITTERMAN: I can stay briefly, yes.

DR. LoCICERO: Our next speaker is Cheryl Leeman; is that correct?

MS. GREEN: No, it's Bettye Green. Sorry for the inconvenience.

I'm Bettye Green, and I'm the president of African-American Women in Touch cancer group, and I'm also a breast cancer survivor.

I believe breast cancer patients deserve more information than they're getting about the risk of breast implants. New research is urgent and needed and disseminated to all. The big question is, who gets the

information?

Case in point. I am in management in my hospital. I was given all of the information before my surgery, whereas an underserved woman was given none. This has to stop. All need the information, correct information.

More than three out of four breast cancer patients are eligible for lumpectomies. That means that most of them need to undergo a mastectomy in order to live a long and healthy life.

Research conducted by Dr. Julia Rowland of the National Cancer Institute found no difference in the quality of life of women who did not have reconstruction after having mastectomies, and according to a study of women who had reconstruction five years earlier, most implant patients were no longer satisfied with how they looked.

So what are the benefits to cancer survivors? As a cancer survivor, a nurse, and a leader of a national group for breast cancer patients and an implant patient myself, I can tell you that most breast cancer patients don't tell their plastic surgeon that they're unhappy. After all, they lived through the cancer. Most don't like to complain about how they look now, especially in the study, when being honest will not help them in any way and could potentially harm the relationship with their doctor. Women still want to please the doctor more than themselves. He is the doctor.

But FDA announced that there seems to be an increased risk of

lymphoma, called ALCL, among women with breast implants. Obviously, the last thing a cancer patient wants is to increase her risk of lymphoma, which is a cancer of the immune system. This was spoken of this morning by the FDA and the statement that further studies will be done. This is a good thing. But it does need to be restated because the women that will be truly affected will not get the information.

Although it is rare, this is something to be very concerned about, especially for African-American women. African-American women are at an increased risk of autoimmune diseases. This finding about cancer of the autoimmune system, therefore, is of great concern to all women.

When the two implant companies did their initial studies of silicone implants and saline implants, they intentionally excluded women with autoimmune disease or a family history of autoimmune disease. There was a reason why this occurred. The companies were concerned about finding greater health risks for their patients.

In fact, Allergan also excluded people with an autoimmune history when they studied gastric lap bands, which are also made of silicone.

However, in the breast implant booklet available on the FDA website, which is 45 pages, there is only a vague statement that safety has not been established for women with autoimmune disease. This is unacceptable.

The FDA should require studies of the possible risk of breast

implants for women with autoimmune symptoms to diseases or they should have a very clear black box warning telling women with these symptoms or family histories that implants may be unsafe for them. Saying that safety is not established doesn't clearly convey if there is a reason to be concerned.

Independent researchers found that the majority of implant reconstruction patients are not satisfied five years later. These findings are more credible than those funded by implant companies. The question is, why aren't they satisfied?

The bottom line is safety research needs to be greatly improved. Women with autoimmune diseases or family history of autoimmune diseases should be included in future breast implant research. Meanwhile, there should be a widely publicized, clear warning of the risk to such women before they can make their decisions to get implants. Women need to be informed of all the pros and cons of silicone and saline implants before surgery.

Thank you so very much.

DR. LoCICERO: Thank you. We're going to take questions now. Everybody can get up.

Dr. Zuckerman, is your center a member -- a partner of the FDA MedWatch?

DR. ZUCKERMAN: We certainly notify people about MedWatch. I don't know that we're --

DR. LoCICERO: You're not a partner?

DR. ZUCKERMAN: Not a partner, no.

DR. LoCICERO: Okay. For the next presenters, did Kathy Nye, Pam Saraceni, or Anne Stansell report their complications to the MedWatch?

DR. ZUCKERMAN: They have notified the FDA, and I know they made an effort to notify MedWatch, but I don't know how successful that was and how many times with, you know, the various -- I'm sure they wouldn't have it done it more than once, not for each problem they had.

DR. LoCICERO: Ms. Linda MacDonald Glenn, is your institute an FDA MedWatch partner?

MS. MacDONALD GLENN: I believe that they are.

DR. LoCICERO: They're not on the website.

MS. MacDONALD GLENN: They are not -- okay, I will -- and neither is Albany Medical Center.

DR. LoCICERO: No.

MS. MacDONALD GLENN: Well, thank you for letting me know.

DR. LoCICERO: Dr. Gitterman, are you representing yourself or anybody else?

DR. GITTERMAN: Yes, as I stated, I'm speaking as an individual.

DR. LoCICERO: Okay, thank you. Ms. Green --

MS. GREEN: Yes.

DR. LoCICERO: -- is your organization a member of the FDA

MedWatch? Are you a partner?

MS. GREEN: No, not to my knowledge.

DR. LoCICERO: Thank you. Did I miss anybody? Are there other questions from the Panel? Dr. Connor.

DR. CONNOR: So I'm looking at the protocol for the core study, for instance, and I can't find an exclusion criteria for Allergan, is history or risk of autoimmune disease. So maybe they can -- I mean, that's a comment that I'll let Allergan maybe speak to that later.

DR. LoCICERO: Dr. Mount.

DR. MOUNT: I actually had a comment. There are no surgical procedures that may be allowed or done on anyone less than 18 without a parental consent. Below the age of 18, a person cannot give their own consent unless they are an emancipated minor. And that's my only comment.

DR. LoCICERO: Other comments or questions? Dr. Leitch.

DR. LEITCH: Dr. Zuckerman made the comment that there were -- I'm sorry, not you, the pediatrician. I'm sorry. Did he leave? Oh, okay. All right.

DR. LoCICERO: Other comments?

(No response.)

DR. LoCICERO: I'm sorry, this is Open Public Hearing.

Okay, we're ready for the next speaker. It's Cheryl Leeman, I hope.

MS. LEEMAN: Yes. Good afternoon. I flew in this morning from Portland, Maine. By way of a disclaimer, I am not here in any official capacity with regards to my employment with the U.S. Senate. Nor am I here with any particular group. I have come at my own expense, on my own personal vacation time, because I feel this issue is that important and the decisions that you make are that important. I come here today to share with you my real-world experiences as a victim of an autoimmune condition associated with my breast implants.

Until July of '07, I was a healthy person. I was a healthy person all my life. Then I was diagnosed with breast cancer; two lumpectomies, a double mastectomy, seven days in the hospital on a heparin drip for blood clots in both my lungs, a year on Coumadin, a pulmonary infarction, two visits to the ER, and finally, finally in July of '08, reconstructive surgery with Allergan silicone breast implants; the worst year of my life, but I thought it was over. Or I thought it was over, which is what brings me here today.

Based on my personal experience, I ask you to establish criteria for future studies that ensures reliable data. And I ask that you establish requirements for both the manufacturers and doctors to inform patients of the potential health risks of silicone implants. Please consider setting the highest standard of safety for women and allow us, allow us to have the best information so that we can make informed decisions.

For almost three years I have suffered from unexplained health

problems, undiagnosed or misdiagnosed illnesses such as hair loss, dry eyes, fatigue, muscle ache, only to find out quite by accident that it was all related and associated to my silicone breast implants. No one told me, no one told me that I should be on the alert for certain autoimmune symptoms. Quite the opposite.

When I asked about silicone breast implants, because I remembered that years ago there was a controversy, I was told there was no longer a problem and they were more natural than the saline. And after all, the FDA had approved them, so they must be safe. I trusted that the silicone implants, because they were approved by the FDA and what I was advised by my doctor, were safe.

Every woman deserves a clear explanation of the ramifications of her choice of implants, and it is up to the FDA to let us know, to let us know what the potential hazards are. If the FDA truly is committed to protecting and promoting your health, as you indicate on your website, then you have a responsibility to protect us, as consumers, by letting us know what is known and what is not known.

I was a healthy person who survived breast cancer, only to end up with an autoimmune condition that has wreaked havoc with my life, as I suffer every day with joint pain and fatigue, and I never know what's going to hit me next because of all of the bizarre health issues that have just been, quite simply, unexplainable. And now I'm looking at more surgery to remove

the breast implants and the related high risk of surgery, given my past history. I feel betrayed. I feel betrayed by the doctors, by the manufacturers, and by the FDA for not being more responsible in protecting my health and that of millions of other women, especially breast cancer survivors.

It's quite simply wrong on so many levels, and I feel this Advisory Panel has a huge opportunity to right a wrong. Do the right thing and act to protect American women, in particular concerning the public safety issues and the reliability of the studies.

I ask you to put in the context of how your decisions could affect one of your loved ones, a mother, a wife, a daughter, someone you care about. Look at the facts and please make the right decision to protect us. Thank you.

DR. LoCICERO: Thank you. Next is Judy McCaul.

MS. STEBBINS: My name is Juliana Stebbins, and I am reading this statement for Judy McCaul, who cannot be here today.

"In September 2007, I had a double mastectomy. I had been scheduled to have my thyroid removed at a time that I found my lump, but I was obviously postponed. About six months later, my plastic surgeon recommended silicone breast implants. I was interested in having a flap surgery using my own tissue, but since there wasn't any surgeon versed in doing free flap in my state at the time, I was not opposed to having implants because I was assured they were safe. My plastic surgeon advised me that if

there any problems, it would be easier to remove the implants and have flap surgery than it would be to correct a problem with flap surgery.

"Three months after I got my silicone implants, I started to feel horrible. I was terribly tired and achy, making it difficult to move. My husband commented that I seemed like an old woman, though I was only 48. Something was obviously very wrong, but I had no idea what. I had no reason to expect that the implants were the cause of my symptoms. I looked into a number of possible causes, including bone cancer, the tamoxifen I was taking, my thyroid replacement, depression or a moodic disease. When nothing I or my physicians tried worked, I began to suspect the implants.

"I decided to have my implants removed and my breasts reconstructed using the DIEP flap surgery. Initially, my health insurance provider agreed to cover the deep surgery, but I was surprised when, despite my surgeon's and my doctor's approval of my choice, my provider changed its mind and decided not to cover deep reconstruction after all. The provider argued they had already paid for breast reconstruction once and there was no proof that it was my implants making me feel so terrible.

"I told them that the way I felt with silicone breast implants was worse than when I was on chemotherapy. And, finally, after going back and forth with them for almost a year while I was in poor health, they agreed to pay for deep reconstruction if I could prove that the implants were causing my pain. If after the implants were removed and my symptoms stop, they

would consider the proof and cover the deep surgery.

"I had my silicone breast implants removed in August 2010. Exactly one week after they were removed, I woke up and felt like my old self again. This past January I had a successful deep reconstruction. This is definitely a difficult surgery, but I feel better than I had in about three years.

"I was never told that a woman with thyroid problems could have an autoimmune disease that makes them more vulnerable to health problems if they get breast implants. It was only when I was preparing my statement that I learned that the patient booklet required by the FDA says that the safety of breast implants has not been established for women with autoimmune diseases. I might've been given the booklet at the time I was fighting my breast cancer, but this was an extremely difficult time and I was researching and reading a lot of material. One small statement, all that material, would not have had a significant impact.

"I wish I was here to ask you to make sure that research is done to determine if breast implants are more risky for women with thyroid conditions or other autoimmune systems or conditions. It seems that the FDA requirements are getting ignored by the implant companies, and I don't believe plastic surgeons want to believe that implants may be causing women health issues.

"Meanwhile, the FDA needs a better warning than the one sentence on page 12 of a patient booklet that most patients never see.

Additionally, I wish you were also the insurance commission because no one should have had to fight their insurance for their health.

"Thank you for your time."

DR. LoCICERO: Thank you. The next speaker is Dr. Susan Wood.

DR. WOOD: Hello, I'm Susan Wood, and I have no financial conflicts of interest. I am currently Associate Professor of Health Policy at the George Washington University School of Public Health and Health Services. Formerly, I was director of the FDA's Office of Women's Health and have worked at both HHS Office on Women's Health and as science advisor to the Congressional Caucus for Women's Issues. My training is my Ph.D. in biology, with postdoctoral research training in neuroscience at the Johns Hopkins University School of Medicine.

First, I want to thank the FDA for convening this very important Panel because the issues and the data that you're evaluating is very important, and it's very appropriate that you be looking at this with a very critical eye.

I've been involved in the issue of breast implants since 1992, when FDA issued the moratorium on both saline and silicone implants back then. But since long before 1992, the question has always been, what does the data show? FDA has been asking this question and asking the companies, different companies over time, to provide adequate data of safety and

effectiveness, and unfortunately, time and time again, the data has come up short. After the 1992 moratorium, the IOM, of course, did its study, also commissioned by the FDA, to evaluate the data at that time.

In 2007, after, you know, the time of approval of the current batch of implants, Dr. Scott Spear, a plastic surgeon at Georgetown, who many of you may know, who's worked for a number of the companies as a consultant, wrote with me an article, which I believe you all have, called "What Do Women Need to Know and When Do They Need to Know It?" This was two people coming together to try and find a common ground about what women should know as informed consent, when you're talking about an implanted lifetime device that won't last a lifetime.

So we were trying to outline and identify the fact that there was still a great deal, at that time, that was not known and that was due to lack of data, and that the difficulty existed for physicians and for women, about how to deliver or to receive true informed consent, again, for this lifetime decision for an elective procedure.

So the questions were: How long will they last? Well, that could not be honestly predicted without long-term data, and I believe that's still the case today.

What are the outcomes, long-term, for reconstruction patients in particular? Again, I don't think, four years later, we still have adequate data to answer those questions.

There is no good data on women of racial and ethnic minorities. And although in the summary paper it argues that there's adequate representation of racial and ethnic minorities in the studies, frankly, that is not the case. When you have three percent African-American inclusion in the study population, that's not going to provide either enough numbers, nor is it representative of the population at large. And yet we know there are racial differences in autoimmune disease and reaction to surgery in different populations.

What is the interaction of silicone implants with the immune system? That's been identified by previous speakers. This is important for women with immune disorders or at elevated risk for immune disorders. And, again, we have no answers.

What is the relationship to the risk of rare events, including cancers, both rare and common cancers? Again, we have very limited evidence on that.

So for more than 20 years, FDA has been asking manufacturers to conduct and report rigorous studies and data on the safety and effectiveness of breast implants, and time again this has not been met.

So this Committee, I am sure, is very aware of the limitation of the current postapproval studies. There was slow recruitment, there was extensive loss to follow-up, which is unacceptably high in most cases, and leaving us with questions about, are the remaining numbers adequate? Do

they represent the study population or is there a bias? Is the falloff rate coming disproportionately from women which have problems? We don't know the answer to that question.

So it clearly limits the ability and it affects the quality of the data for both, not just for the long-term questions but for the short-term questions. If your population is biased in terms of who is in it, then even your short-term numbers could be wrong, much less not having adequate numbers for the rare events or long-term outcomes.

DR. LoCICERO: Can you sum up, please?

DR. WOOD: Yes. So this leaves us very much in the place that we were in in 1992 and before. So women are getting these implants. FDA approved these products on the condition that they are complete, adequate postapproval studies, but these studies do not meet the bar.

So I have the following recommendation: that FDA should enforce these requirements to the maximum allowed under law and regulation, and these real enforcement mechanisms and penalties need to be in place, and they should include consideration of withdrawal of approval, requirements for sponsor-funded but independent research conducted to answer some of these questions, significant financial penalties, major labeling or patient information changes, or restricted distribution.

Again, I thank you.

DR. LoCICERO: Thank you. Our next presenter is Nicole Noll.

MS. NOLL: Hi, my name is Nicole Noll. I have no financial interests in the outcomes of this hearing and have not received any compensation. Thank you for allowing me the opportunity to speak about my experience with silicone breast implants.

I am a 35-year-old mother of two. I work full time as a sales representative and had thought about breast augmentation for several years and actually had a consultation about six years ago. And due to my small frame with basically very little breast tissue existing before my augmentation, I decided to wait until silicone was an option for me. And there were several personal reasons for that, but I just -- after my two children had lost virtually all my -- any volume that I had in my breasts and wanted to restore some self-confidence and be a little more proportional.

So after doing a lot of research, several different consultations with different plastic surgeons, I decided on a surgeon and was given all the risks and benefits, to risks and complications to breast augmentation and the choice of silicone versus saline. I personally opted for silicone because I wanted a natural look, I felt that the silicone was a softer feel and felt more natural, and because I really had no existing breast tissue, I was concerned with saline, about their rippling side effect and also that it was going to be more visible than the silicone implant.

I had a great experience. If I had to do it all over again, I would absolutely make the same decision that I made and get the silicone breast

implants.

I feel that the recommendation of the post-implant MRI is unnecessary, it's a large expense for a patient to undergo, and with the risk of a false positive, you could end up getting an unnecessary surgery. Thank you.

DR. LoCICERO: Thank you. The next speaker is Ruby Rahn. No? No Ruby Rahn.

Next is Shara Thompson. No Shara Thompson.

Next is Janice Erickson. Please state your name because I'm getting confused.

MS. ERICKSON: Thank you. My name is Jan Erickson, and I am testifying here today in lieu of my president of the National Organization for Women. I am testifying for our foundation. We have long followed --

DR. LoCICERO: Please tell us what organization.

MS. ERICKSON: The National Organization for Women Foundation. And we represent only our own supporters and have no conflict of interest in that regard.

Over the years, we've heard from countless women who are saline and silicone breast implant patients and who have suffered from complications involving both long and short-term health problems. I don't need to reiterate that long list of the complications that these women have suffered from as this Committee knows well what those are.

I think it's important to remind the Panel that National Cancer

Institute studies indicate that women who have breast implants are at increased risk for brain cancer, lung cancer, emphysema, pneumonia, and suicide. Although research paid for by implant companies disagrees, those findings need to be evaluated by independent researchers. And now we learn that a rare type of immune system cancer, anaplastic large cell lymphoma, is found at rates higher in women with implants than in women without breast implants.

NOW opposed and continues to oppose FDA approval of silicone gel-filled implants, convinced that the risks clearly outweigh benefits. A number of FDA staff and Advisory Committee members agreed with us at the time of approval. We've testified numerous times before FDA committees on the need for well-controlled, independent, long-range studies that closely track a significant number of patients. NOW was then and remains of the opinion that companies have little motivation to carry out rigorous long-term evaluations of implant patients, and the experience since the 2006 approval of the silicone gel-filled implants confirms our view.

It's important to note that, in January 2004, the FDA found that Inamed, now Allergan, had failed to provide long-term safety data on silicone gel-filled implants. Companies have now had 18 years to collect long-term data on patients. The problem is always the same: too many implant patients drop out of the studies or, more accurately in our view, the companies fail to carry out an effective surveillance in implant patients.

It is unacceptable that, again, a substantial number of the 40,000 patients that Mentor and Allergan were required to track were lost in just a very short time frame. Mentor had lost track of 79 percent of all patients within three years of their enrollment, and Allergan lost track of almost half of their augmentation patients within the first two years. I think some of these other failures have been described by other witnesses here.

Such a high loss to follow-up completely undermines the value of any findings. Patients who dropped out are not likely to participate later. Yet we know from patient testimony at past FDA meetings that symptoms often develop 10 or more years after implantation.

In this connected universe, with the internet, e-mail, and Facebook, it's hard to believe that companies were not able to maintain contact over time with a larger number of implant patients. They could have, for example, provided stronger incentives for patients to stay in the studies, as is done in other research.

Other witnesses will testify to problems, errors in the material that's been provided by the companies. But I think it's important that NOW has concluded, after reading these materials, that several steps must be taken.

We believe that approval to market silicone gel-filled implants for one company, Mentor, should be rescinded right away. With regard to Allergan, a moratorium should be placed on further marketing implants, and

the company should be required to continue research with an improved study design and heightened FDA oversight. If Allergan is not able to improve its patient follow-up within two years, then approval to market their silicone gel-filled implant should also be rescinded.

There remains a continuing need to conduct clinical and laboratory studies on the immunological and toxicological effects of silicone gel on human physiology. We need properly designed studies that measure the effect of the chemical constituents of silicone gel in pregnant women and their developing fetuses. We need information about the transmission of potentially harmful chemicals to breast-feeding infants. Clinical trials should follow children born to mothers with silicone gel-filled breast implants to evaluate any health or developmental problems. All of these recommendations were made previously by the National Organization for Women to the FDA.

In addition, a series of research recommendations were made at a symposium on the safety and effectiveness of silicone gel-filled breast implants in July 2003, which we are also submitting to the Panel today. Most of these research needs are, to our knowledge, today unmet. Thank you.

DR. LoCICERO: Thank you. We're going to have some questions at this point.

Ms. Leeman, are you a member -- are you a participant in any of the follow-up trials? Or have you reported your problems to the FDA

MedWatch?

MS. LEEMAN: Let me answer the first question first. When I got my booklet from the manufacturer, the informational sheet that invites you to participate was folded over and paper-clipped to the inside. I was never asked if I wanted to participate. That's number one.

Number two, when I did call on their 800 number to inform them that I was having problems and could I get into their study, I was told that the study's -- participants for the study could no longer get in because they had closed off the trial period.

I do have the form for MedWatch. I'm in the process of filling it out. But you have to take a look at it to understand why people don't fill it out. It's a cumbersome form. It's confusing. And I feel I'm a pretty smart person. But the information that they're looking for is not the information that you can necessarily glean from the problems that one might be having. So that form, in and of itself, needs to be revamped so that it's more consumer-friendly. And there needs to be a place where folks who are not in the study can go and let folks know what's going on. Thank you.

DR. LoCICERO: Thank you. Ms. McCaul, the same question.

UNIDENTIFIED SPEAKER: I can speak to that. She's left, but I'm familiar with Ms. McCaul as well. I'm sorry, what was the question?

DR. LoCICERO: The question is, was she a participant in the trial? And if she was not a participant in the trial, did she report to the FDA?

UNIDENTIFIED SPEAKER: She was not a participant in the trial, and I'm not aware of whether she reported, but I could get that information for you.

DR. LoCICERO: Thank you. Ms. Noll --

MS. NOLL: Yes.

DR. LoCICERO: -- are you a participant in the postmarket trial?

MS. NOLL: No.

DR. LoCICERO: If you were to have a problem with your implants, do you know how to report to the FDA?

MS. NOLL: Yes, yes.

DR. LoCICERO: Thank you. Ms. Erickson, has your organization developed any mechanism for your members to report their issues to the FDA?

MS. ERICKSON: We have an informal referral service to another NGO that works more closely on this issue, and we put information on our website about what patients should do to follow up.

DR. LoCICERO: Any questions from the Panel?

(No response.)

DR. LoCICERO: Okay, I think we're ready to move on. Please.

MS. FAUCETTE: I'm sorry. You made a mistake on the name just a moment ago. You said Shara Thompson. It's Jane.

So my name is Judith Faucette, and I'm here to read for

Jane Thompson, who has no financial relationship with any group or company that may be affected by silicone breast implants.

"After 16 years with my textured Meghan saline breast implants, I opted to make the switch to Allergan's new cohesive silicone gel breast implants in July of 2010. I'm in the Allergan study.

"Almost immediately I began to feel quite ill. I had extreme fatigue, numbness and tingling, nausea, dizziness, heart palpitations, hair loss, depression, severe insomnia, ringing ears, weakness, stomach and headaches, and anxiety.

"Around 90 days after implantation, other major symptoms appeared: chest pain, lymphadenopathy, uncontrollable tremors, vertigo, widespread severe muscle and joint pain, symptoms similar to MS, difficulty swallowing, drooling, liver pain, loss of peripheral vision, symptoms of interstitial cystitis, severe skin tightness, face pain and lockjaw, vomiting, diarrhea, and dry throat and eyes. I developed several ovarian cysts, stopped menses during this time, had tongue swelling, facial swelling, difficulty breathing, low white cell count, memory lapses, and suicidal thoughts. I lost 20 pounds in three weeks. I became completely dependent on my family and friends. These were symptoms which I had never had before, all of which developed in the short time I had Allergan cohesive gel breast implants.

"Prior to receiving these implants, I had only seen my doctor twice a year for a refill of thyroid medication or the occasional minor illness

or cold.

"I had my implants surgically removed five months later in December of 2010 and immediately the symptoms started to disappear. Ninety percent were gone immediately, and the remainder of symptoms disappeared over the next few weeks.

"There are no words to fully describe the horrific experience these new cohesive gel silicone breast implants caused me and my family. I received no warning about the possibility of the gels triggering my immune system and causing life-changing disease.

"I saw a total of five doctors during the time of my implants, including two from the Mayo Clinic, and they all believed that the implants stimulated my immune system. Not one of these doctors doubts that I had a very strong immediate reaction to silicone gel.

"My terrible autoimmune reaction was reported to Allergan, but in their records they falsely stated that my autoimmune symptoms occurred before the implants, not after. The report states, 'There is no complaint against the devices. The patient has a history of multiple medical concerns prior to implantation.' That is completely untrue.

"Prior to my gel implants, I had a minor thyroid problem that was under control. After getting cohesive gel implants, I had very serious autoimmune symptoms that were completely devastating. It wasn't until my gel implants were removed that I learned that Allergan excluded from their

breast implant study any women with any kind of history of autoimmune symptoms, either family or personal history. That information is not widely available, but it is listed as a 'precaution' on page 12 of the Allergan patient booklet, which states that safety has not been established for women with autoimmune diseases. This booklet is considered labeling that the FDA supposedly requires plastic surgeons to give to patients, but I never received a copy.

"There should be a very obvious warning for women with any kind of personal or family history of autoimmune symptoms or diseases with a black box around it. Instead, the FDA included the above vaguely worded precaution, which did not explain that women with autoimmune diseases were intentionally excluded from studies because of concerns about how their health might be harmed.

"Since the FDA didn't require that information, neither of the companies nor the plastic surgeons are warning patients. And earlier this summer, the FDA went on record as saying there was no proven link to autoimmune diseases without even mentioning that the implant companies excluded women with autoimmune symptoms or history from breast implant studies.

"This is an outrageous situation. I was terribly harmed by my implants. A black box warning would've persuaded my doctor that I was at risk of health problems from breast implants because of my thyroid condition.

"I was lucky that the link to my implants was so obvious, but what about women who have mild or even moderate reactions? It might not be obvious to them or their doctors. Or, even for women who have an obvious reaction, remember that some of these women wouldn't be able to afford to have surgery to have their implants removed. You can get implants put in on an installment plan, but if you want them removed, you need to pay for the surgery.

"There need to be clear warnings about the dangers of silicone gel breast implants so that women can make an informed decision on whether or not to take that risk. And the research that you require on implants needs to focus on the kinds of autoimmune symptoms, such as the ones I described, that women with implants are reporting.

"Thank you for your time."

DR. LoCICERO: Thank you. The next speaker is Dr. Susan Cassidy.

DR. CASSIDY: My name is Susan Cassidy. My perspective is as a physician with a degree from Vanderbilt Medical School. I'm a board-certified internist. I've had a focus on women's health issues, and I have a family history of breast cancer, both on either side of my family; mother's and father's sister both died of breast cancer. No one's paying me to be here. I'm not representing any institution, foundation, or company, and I'm here at my own behest and have no conflict of interest.

I would like to address some data issues just from the perspective of a physician who's used to reading data and journal articles and wondering what to make of the data that has been presented.

I refer you to page 17 of the Executive Summary. In there the FDA notes, "As follow-up has lagged, FDA recognizes that the studies may not provide data necessary to answer questions about rare associations." Well, I would argue that with a large number of women lost to follow-up, it also makes it very difficult to draw meaningful conclusions about other issues like safety and complications.

You know, significant numbers of patients we've heard over and over again. It's been noted that they've been lost to follow-up in the postmarket studies, and it really remains unclear, then, if the women who continue to be enrolled in these studies are truly representative of women with implants in general.

You know, how does an individual woman considering silicone breast implants know the likelihood of experiencing serious complications for herself? And I think I read these studies with that question overarching in my mind.

You know, one of the things I noted was the asymmetry rates, and I particularly am familiar with the reconstruction patients with implants. Rates in reconstruction patients are typically reported in excess of 50 percent asymmetry with implant reconstruction. And yet Allergan reported rates in

reconstruction patients of about 23 percent, and Mentor's submission does not include any data on asymmetry in reconstruction patients. So while that may not be the most important issue we're talking about here, to me it was a measure of the quality of the data.

You know, studies need to include data on mammogram risk, the risks of rupture, the need for additional views for mammography. You know, the low MRI rates are kind of expected unless, as part of the study design, coverage is provided for women. We talked about the $2,000 expense. I think it's pretty expected that there will be low follow-up.

You know, there's a need for capturing data about complication rates with the aging population. I mean, we are soon going to have hundreds of thousands of women in their sixties, seventies, and eventually eighties with implants in this country that are hardened and/or may need to be replaced. And where are we capturing the increased risk of surgery in aging women with comorbid medical conditions, who, you know, may need their implants replaced? Forget about the cost of that to our healthcare system.

I think that there needs to be some focused studies on safety issues of silicone implants, particularly in reconstruction patients with cancer. I think they're a very different population, perhaps, than the healthy individual, just like the aged population is a very different population than the young, healthy woman who decides to have augmentation with silicone implants.

I think the studies need to be extended in their length. I think they need to capture age-related data as well as data about rare complications. We need to enroll more studies, there needs to be a longer interval of study time, and I again, as well as some of the other speakers this morning, support the need for independent research by the FDA. Thank you.

DR. LoCICERO: Thank you. Our next speaker is Margaret Dunkle.

MS. DUNKLE: I'm Margaret Dunkle, Senior Research Scientist at the Department of Health Policy at George Washington University. I've received the American Academy of Pediatrics Dale Richmond Award for outstanding achievement in the field of child development and Vice President Al Gore's Reinventing Government Hammer Award. I have testified nine times before Congress on issues affecting women, children, and families, and have more than 100 publications.

I am here today solely because of my interest in ensuring that medical products for women be proven to be safe and effective. I'm not representing any organization. I am not being paid or otherwise compensated.

The 2006 FDA approval of silicone gel breast implants was controversial because there were so many unanswered questions about the long-term safety of these implants, including when they might break and leak inside a woman's body and what the consequences of such leakage might be.

As conditions of approval, the FDA required that the two implant companies, Allergan and Mentor, each study at least 40,000 women. The FDA also required that these studies be at least 10 years long, since some adverse consequences are not obvious or even measurable in fewer years. It takes both time and a large sample to identify subpopulations of women who might be at great risk for problems. It is now five years later, but the data for both Allergan and Mentor studies are not what they need to be.

Why do I say this? Because of the extraordinarily high loss rate of study participants. In just three years, Mentor, now a subsidiary of Johnson & Johnson, has somehow managed to lose four out of five of both the silicone implant patients and augmentation patients enrolled in its 10-year study. This paltry enrollment rate, with only 21 to 29 percent of patients still in the study, makes their data virtually useless in terms of assessing either safety or effectiveness.

As you can see, Allergan's rates are better, but they're still low. Simply put, when you lose half or more of your sample, you cannot assume that the data for the few left also represent those who were lost. The Mentor rates would be laughable were it not for the seriousness of these issues.

Let me put it this way. If I can find my antediluvian high school classmates with a few clicks on Google, why can't these well-resourced medical device companies find people that they have already consented and identified into clinical trials?

So what to do about this bad situation? The FDA's job is to protect the public health by ensuring that such things as medical devices implanted into women are both safe and effective. My five recommendations are aimed at doing just that.

First, rescind approval of the Mentor implants. They did not uphold their part of the bargain for the postapproval study. If they cannot competently do the research to ensure their product safety, they should not be putting their products into the bodies of more than 100,000 women every year.

Second, do not restore Mentor approval until they have at least two years of credible data with 80 percent or more retention of clinical trial recipients. They could accomplish this by reenrolling or finding the people that they have lost to the study.

Third, extend the duration of both the Mentor and Allergan study to 15 years. The FDA's own update indicates that 10 years may not be long enough to identify long-term problems.

Fourth, require ongoing transparency and disclosure of the data, hold more public meetings such as this, and issue regular update reports.

Fifth, implement a broad FDA policy to put companies on notice that there will be consequences of not doing or incompetently doing FDA-required postapproval research. Consequences could include withdrawing

the product from market or substantial financial penalties.

In conclusion, with almost 400,000 women every year getting breast implants, these studies need to be done right.

Thank you for this opportunity to comment.

DR. LoCICERO: Thank you. Our next speaker is Dr. Edward Melmed.

DR. MELMED: My name is Edward Melmed. I'm a plastic surgeon in Dallas, Texas. I'm board certified in England, Scotland, South Africa, and the United States, and I'm not doing any more.

(Laughter.)

DR. MELMED: I'm going to speak to you purely as a clinician in private practice and to base my emphasis on the cost-to-benefit ratio.

There's only one good thing about breast implants for augmentation: big boobs. All of the rest we have to decide about today is, is it worth it? To date, I have removed over 2,500 implants, ranging from rotten to disgusting, that have worn out over the period of time, not to mention many of the illnesses that women have complained about.

Jack Penn in 1968 said, Augmentation is not an operation. It is a procedure. You make a big cavity, put in a large foreign body, everyone has a complication, and everybody's happy. He wasn't far wrong.

There are basically four major problems with implants. The first is rupture. I will discuss this further in a second. The second is capsule

formation. Every foreign body in the body, every foreign body, whether it be a suture, a BB pellet, shrapnel, gets encapsulated. We all know the long-term complications of capsule formation. The third is the aesthetic deformities that are created by the latest aberration following on the internet, at least on television programs, and this is what I commonly see in my practice: a woman with breasts that look like this, that are absolutely revolting, rock hard, deformed, painful; and I could go on.

Symptoms. We've heard a lot from all of the women here. I just wanted to say something about symptoms: they are real. I do not have a website, but I answer five to seven e-mails a night from women all over the world, the latest being from Natasha in Russia, from Heidi in New Zealand, and they all are seeking advice. What do I do? I've got this fatigue, short-term memory loss, brain fog. You've heard it all. It's real.

The water was muddied by the lawyers when they put in their claims about classical autoimmune disease. This is a variant. And I spoke to Charles Haley, who, as you know, established that Gulf War Syndrome was a valid disease. The symptoms that women have are very similar, minus some of the gastrointestinal symptoms, but are very similar, and our combined opinion was this is some form of "industrial toxin."

First, I'll just briefly talk about the problems with saline implants. The average lifespan is 12 to 14 years, and then they rupture. Okay, that's fair enough. When we put in IV saline, it's got an expiration date,

as you can see in the top right-hand corner. To the best of my knowledge, the saline in an implant has no expiry date. What? There's no expiry date? The fluid is put in through a bag.

And there's no literature that I'm aware of. There's reports on the culture of saline in long-term implants. What happens to the fluid when it ruptures? Well, this is an implant I took out the other day, which is full of fungus. Where did the fluid go?

Rupture, in my experience -- and I wrote this up in 1998 -- 50 percent of implants were ruptured by 10 years, 72 percent by 15 years, and 20 percent by -- at least 94 percent by 20 years. That figure has not changed, and in the right-hand little picture you can see the advanced calcification in a ruptured implant.

Now, you have to just think about this. You're going to put an implant into -- a silicone implant into a 22-year-old. What is it going to be like down the line?

Taking the implant out. That was supposed to be a video. It is not playing, and I apologize about that. But the liquid silicone will just pour out of the older implants. It just literally comes out.

Other problems, major problems with gel implants is the deformity, the contracture rates. Most implant ruptures are silent. We've already established that. And most occur after 10 years. How can a two-year or a three-year study that has been asked for demonstrate anything? It

doesn't.

Capsular contracture is an incredible deformity, and it causes pain. Women can't lie on their tummy, they can't hug, they are just -- it's a ghastly situation.

Other major implants. When the implants are put into the sub-muscular position, the pectoralis muscle is released in my studies of explantation. The pectoralis that is divided retracts and is useless. They always have this sub-muscular deformity when they contract the arms.

DR. LoCICERO: Can you sum up, please?

DR. MELMED: Sorry?

DR. LoCICERO: Summation.

DR. MELMED: Can I just quickly go through this, then? Okay -- in Holland said, If we had a policy to replace implants after 10 years, whether they need it or not, there'd be no silicone issue.

I just want to briefly mention difficulty in follow-up. In my own practice, I keep every medical record I've had since 1975. My follow-up was nine percent. I don't believe I'm different from any other physician. Patients, they're mobile, they change names, they get married, they get remarried, they're divorced, and they disappear.

I want to just finish and finally say to you, why has FDA continued to allow a device that has guaranteed 80-percent failure rate? You wouldn't do that with a hip joint. Why is it allowing a woman to have this?

It's an abuse of women to guarantee all of these complications. And I question, would the FDA allow this if it was in men? Thank you very much.

DR. LoCICERO: Thank you. The next speaker is Dr. Jeffery Kenkel.

(Feedback noise.)

DR. KENKEL: Okay. I'm normally a very quiet and reserved gentleman, so that's quite an introduction.

(Laughter.)

DR. KENKEL: As I mentioned, I'm Jeffrey Kenkel. I'm president of the American Society for Aesthetic Plastic Surgery, also known as ASAPS. I'm a board-certified plastic surgeon. I'm professor and vice chairman at the University of Texas Southwestern Medical Center at Dallas.

I appreciate the opportunity to speak with you today. I've got no conflicts to disclose and have no relationships with any implant companies. My travel expenses have been paid for by ASAPS.

On behalf of our organization, we would like to applaud the FDA's ongoing mission to protect the safety and well-being of our patients. We appreciate the opportunity to be a part of this important assessment of the postapproval study for SGBI.

Our members are board-certified aesthetic plastic surgeons from North America and around the world. The cornerstone of our mission is education, both physician and patient. Our society has enjoyed a

collaborative educational effort with both industry and the FDA regarding breast implants and other devices. Working together has allowed us to disseminate important and accurate information that we have been able to disseminate to our physicians and patients about SGBI.

Live and archived lectures and webinars provide our members with the latest information regarding the safety and efficacy of silicone breast implants from both published peer-reviewed articles and up-to-date data from both the core and postapproval studies. Our members are able to synthesize this data and provide their patients with accurate information so they can make appropriate informed choices. This type of collaborative effort benefits all involved.

A healthy candid dialogue among industry, the FDA, and plastic surgeons allows for a candid assessment of where we are now, what we have learned, and how we might make changes in the process to make it more effective and informative.

We all recognize that time allows for ongoing assessment and innovation. Investigation allows us to not only learn about the products and techniques we have and how best to use them, but also creates opportunities to develop new ones that may be able to replace those currently used.

ASAPS, in its research arm, the Aesthetic Society Education and Research Foundation, or ASERF, believe in the power of research, investing in clinically, translational-focused research performed by our members with the

hope of making our patients' lives better.

Let me highlight briefly just a few pertinent projects we are working on. The creation of a detailed aesthetic code and database will allow us to prospectively collect detailed data regarding breast implant surgery, devices, and outcomes. Dr. Bill Adams will highlight Dr. Brad Bengston's work, sponsored by an ASERF grant, using high-resolution ultrasound to accurately evaluate the integrity of SGBI in a simple office setting.

We also organized what we believe to be the first summit of cross-specialty, board-certified plastic surgeons to develop standardized evidence-based rankings in plastic surgery, teachings, and publication. These standards have already been adopted by two of our leading peer review journals, the *Aesthetic Surgery Journal* and *Plastic and Reconstructive Surgery*.

This type of work may allow us to improve the current postapproval studies, providing cost-effective information regarding these devices, while at the same time respecting our patients' privacy and time.

The postapproval studies were developed to help address concerns raised during the approval process. We must work together to ensure their success. New ways to improve patient compliance, enhanced data collection and numbers, and the incorporation of new technology for surveillance that is easy and cost effective, all must be considered.

Change is often made following experience and innovation. We

can use both to improve our success for obtaining substantial and scientifically valid data that will better allow us to answer the questions posed five years ago.

On behalf of the Aesthetic Society, I'd like to personally thank all of you and the FDA for overseeing this postapproval process for silicone breast implants. The collaborative work done in the area has reassured our physicians and patients about the safety of these devices. We are confident that innovation through research and dialogue among all involved will make these types of studies even more beneficial in the future. There's no argument as to our goal: patient safety and a better-informed patient.

Thank you for the opportunity.

DR. LoCICERO: Thank you. The next speaker before we start asking questions is Carolyn Wolf.

MS. WOLF: My name is Carolyn Wolf, and I live in Virginia. I have paid my own expenses and I have no conflicts of interest.

At 41 in 1972, I had subcutaneous mastectomies due to fibrocystic disease, then reconstruction with Dow Corning silicone breast implants. Seven years later, small burning blisters formed on my neck. I stopped wearing jewelry and makeup, even though allergy tests were negative. I continued to develop these blisters, and other implant patients have told me they also had them.

By the 15th year my implants had become very hard. After 17

years I was hospitalized for three days with what appeared to be a heart attack, but the symptoms showed there was no heart attack. I asked the internist, Could this be from my breast implants? And he says no. In hindsight, I think this episode was the result of silicone leaking from my left implant. Three years later, I developed joint problems on my left side, my shoulder, elbow, ankle and foot. Gradually the fingers and toes became numb.

I went for checkups every year at Walter Reed. No suggestion was ever made for an MRI until a bubble appeared on the right implant about 26 years after getting the implants. Because there was a long wait to get the MRI, a radiologist did an ultrasound. The report was no cancer, everything okay. About a year later, I started feeling burning in my scalp. It felt like a red-hot worm crawling along the part line. I also had three episodes when long strings of silicone came out of my ears. Twenty-eight years after implantation, the left breast collapsed fully.

I finally got my first MRI, which showed both implants extensively ruptured. When the implants were removed in 2000, the total material that came out would not have filled a small-sized Styrofoam cup. Obviously, the rest had leaked or deteriorated into my body.

Because of continuing dizziness and brain fog, a brain MRI was performed in 2001. This showed more than 20 lesions on my brain. EMG tests showed much damage to my left eye, to my left arm and hand, and

extensive neuropathy in the extremities. And a doctor who studied at Mayo did those tests.

Three years ago I was hospitalized with giant cell temporal arthritis. So far I have been able to control the inflammation with high doses of prednisone. I am diagnosed with connective tissue disease, multi-nodule thyroid, chronic fatigue, fibromyalgia, PMR, asthma and COPD, MS-like syndrome with neuropathy of the extremities, platinum poisoning. My platinum level is 140, 35 times normal by CDC/OSHA standards. I also have irritable bowel syndrome, all symptoms of silicone adjuvant disease.

I'm not the only woman with this kind of experience. There are still thousands of women who have had leaking silicone breast implants for their bodies for decades. They can't afford surgery to remove them and they don't have insurance. Others like me had doctors who told them that their health problems are unrelated to their implants.

In recent years many of those doctors are saying the FDA says they're safe and leaking silicone doesn't cause problems. And many women believe the doctors and just get sicker and sicker, and many of them just finally give up and commit suicide. And that's not because they don't have two knobs on their chest.

I ask the Advisory Committee to think about how your recommendations will affect these women. Why is there no research focused on the women with leaking silicone implants and what happens to them? The

FDA did such a study 10 years ago. The manufacturers say the newer implants are safer, but there are no studies to prove this because the studies required by the FDA follow women for only 10 years. Is the FDA willing to publicly state that silicone and platinum leaking into women's bodies year after year is safe?

So far, the FDA keeps requiring the companies to do research, but the research is not getting done properly. Women are being terribly harmed as a result. Please make sure that these research requirements are enforced. Thank you.

DR. LoCICERO: Thank you. Before you leave the podium, have your problems been reported to the FDA MedWatch?

MS. WOLF: I made reports in the beginning, right after I had the implants removed, and they used to give out numbers and you could verify that those reports are made. And then you stop making them and I don't think I have made any -- I made one. I never had an acknowledgment that it was received, and I haven't made any more.

DR. LoCICERO: Thank you. Thanks to the representative of Jane Thompson for telling us that she's in the study.

Dr. Cassidy, you said you have contact with reconstruction patients. Have you had patients who have had difficulty with their implants, and if so, what do you advise them about reporting their difficulties to the FDA?

DR. CASSIDY: I do not actively treat the patients myself. I have been involved in the breast cancer issue enough that I get phone calls from people and have done some consulting work in that arena, and in that way I have come into contact with patients that have had unsuccessful implant reconstruction, many of whom with significantly untoward consequences.

And, you know, I have basically advised them to go back to their surgeons to figure out what has to be done, or we'll come up with the name of surgeons that I know are willing to see patients that have had problems because, as others have mentioned before, that is a challenge for some people, to go back to the surgeon with problems.

DR. LoCICERO: Thank you. Dr. Melmed, you say you deal with a lot of these problems. What is your policy in reporting these issues to the FDA, and do you send all of your ruptured implants to the company?

DR. MELMED: No to both of them. This one. No to both. All of my specimens are sent to the lab at our hospital. We have found 100 percent positive silicone in the capsules. The implants are returned to the patient, in whatever form it is, and they are half the time still confused whether there's litigation involved, whether they send it off to the private labs, but I do not report it to the FDA.

DR. LoCICERO: Do you advise your patients to report their problems to the FDA?

DR. MELMED: Yes, sir.

DR. LoCICERO: Okay, thank you. Dr. Kenkel, is your organization a member -- an FDA MedWatch partner?

DR. KENKEL: I don't believe so.

DR. LoCICERO: Thank you. Any questions of any of the other members here? Dr. Leitch.

DR. LEITCH: For Jane Thompson, I was wondering how she received information about the research records that were held at Allergan or Mentor.

MS. FAUCETTE: Um-hum.

DR. LEITCH: Allergan, I guess.

MS. FAUCETTE: She had several conversations with an Allergan representative on the telephone, where the Allergan representative said -- she would say that I've had these issues, I want to report them, she was in the study, and they said -- the representative stated that they happened prior, and each time she corrected. Then she received something in the mail. I believe that it was to explain why she was no longer in the study. At least that's how she explained it to me. I could get you more information, but that was where that quote I read about the multiple -- the quote that said she had multiple health problems. That was not true. That was in writing that she received.

DR. LoCICERO: Dr. Connor.

DR. CONNOR: A quick question to Dr. Melmed. Thank you for

the presentation. I thought that was very interesting. And I'm wondering if you've just done any testifying in lawsuits regarding implants for either, you know, plaintiffs or device manufacturers.

DR. MELMED: I've been sued for it, but I've never testified.

(Laughter.)

DR. LoCICERO: I'm sorry, another question.

DR. CALLAHAN: Leigh Callahan.

I had a question for Dr. Melmed. Do you have thoughts about implants for reconstruction? Your focus was on augmentation.

DR. MELMED: I limited my discussion today to augmentation because that is the majority of the work I do. I do not do breast reconstruction and haven't done it for many years. I do see patients who come in with ruptured implants who have had reconstruction and we'll do the appropriate thing, but I do not do DIEP flaps and I do not do TRAM flaps of all latissimus flaps because that again involves silicone. If they are prepared to have them out and just be flat again or semi-flat, that's what I do.

DR. LoCICERO: Other questions?

(No response.)

DR. LoCICERO: Okay, we're ready to proceed. Next is Dr. Laurie Casas.

DR. CASAS: Good afternoon. I am Dr. Laurie Casas, a board-certified plastic surgeon and Clinical Associate Professor of Surgery at the

University of Chicago Pritzker School of Medicine. I am a member of the American Society for Aesthetic Plastic Surgery, also called ASAPS, and have served as a member of its board of directors. I am a past president of the Aesthetics Surgery Education and Research Foundation, the philanthropic research arm of ASAPS. I have published extensively on breast surgery topics over the past 20 years and have participated in and published two multi-site, prospective outcome studies on patient satisfaction following cosmetic procedures. I have no financial ties to any implant manufacturer. My travel and lodging expenses were paid for by ASAPS.

According to ASAPS' annual statistics, breast augmentation has been the most commonly performed aesthetic surgical procedure since 2008. In 2010, over 300,000 procedures were performed, and of these, 62 percent chose silicone gel implants.

Plastic surgeons are patient advocates. We feel that patient safety, patient education, and patient satisfaction are of primary importance. We strongly believe that a woman's right to choose breast implants is paralleled by her right to be fully informed of both the risks and the benefits of breast implant surgery.

In the real world, patients come in to our offices every day and ask questions like, Will my breast implants last forever or do I need to plan to replace them in my lifetime? What happens if they break and my breasts look and feel fine? Do they need to be replaced? Can you do a safe, reliable

test to see if my breast implants are broken without surgery? Why should I get an MRI at three years after I had the implant surgery if I feel fine and my breasts look and feel normal? Also, why should I get an MRI every two years after that? Isn't an MRI expensive, and who will pay for it? Isn't there a better, less costly test? I have also heard that MRIs sometime show that the breast implant is broken when the implant is fine. As plastic surgeons and patient advocates, we need to answer these important questions.

As a physician and a scientist, we have several outstanding issues that need to be answered in order to give our patients the answer to these clinically relevant questions. Among them are, number one: What is the most effective methodology for data collection so these pertinent questions can be answered? Number two: Are the core, large PAS, and other four postapproval studies enough to answer these questions? Number three: Is the present labeling recommending MRI after three years and every two years thereafter cost effective, and is MRI specific and sensitive enough?

At the present time and in my real world, my patients are not being compliant with the MRI labeling because they state that the MRIs are too expensive, too time consuming, and cause false positive results that can lead to recommendations for unnecessary reoperations.

Moreover, many of my patients have read the published data that states that device failure rates are about half to one percent per year. Then they ask me why should they go through the expense and

inconvenience of having an MRI before 10 to 15 years after implantation if they are asymptomatic and they do not feel any change in the breast implant shape or feel.

Over the past 21 years, I have found that happy, healthy patients who are satisfied with their surgical outcomes do not want to spend their time or risk their anonymity by participating in a study. This creates a huge challenge for plastic surgeons who try to enroll their patients in breast implant studies.

In addition to patient-related compliance and enrollment issues, capturing data on rare events with the current study design is challenging at best and probably impossible. For that reason, plastic surgeons fully support the FDA and our colleagues in the development of an ALCL breast implant registry to better understand this rare event.

Unfortunately, it's becoming clear that the current design of the core studies and large PAS will not effectively and efficiently answer the questions plastic surgeons or patients and the public are asking. We are definitely at a juncture where innovation is needed so that we can continue to answer clinically relevant questions.

We may need to consider utilizing existing international data sources, existing and emerging literature, to supplement the data from ongoing postapproval studies. By analyzing existing robust international registries and existing and emerging literature, we may be able to move

effectively to collect data. Finally, it is clear from our recent experience with the rare event of ALCL that case reports must be reviewed on an ongoing basis and evaluated for their relevancy and data collection.

As plastic surgeons and patient advocates, we're committed to participating and supporting the existing data collection process and helping to improve patient compliance. We look forward to the Panel's input on existing labeling, study design, and how to improve patient enrollment and compliance. It cannot be stressed enough, as plastic surgeons and together with our patients, we are committed to collaborating with the FDA and the implant manufacturers to collect data on an ongoing basis. Thank you.

DR. LoCICERO: Thank you. Our next speaker is Dr. William Adams.

DR. ADAMS: My name is Dr. William P. Adams, Jr. I'm a board-certified plastic surgeon and Associate Clinical Professor of Plastic Surgery at UT Southwestern Medical Center in Dallas, vice president of the Aesthetic Surgery Education and Research Foundation, also known as ASERF, and the chair of their scientific research committee. I'm an investigator for both Allergan and Mentor's cohesive gel implant trials, and an educational consultant for Allergan, and derive income from these relationships based on my time allocated to related projects. My travel expenses today were paid by the American Society for Aesthetic Plastic Surgery, also known as ASAPS, for whom I serve on their board of directors.

My current practice is 90 percent breast surgery, both reconstructive and aesthetic, and I have witnessed firsthand the great benefit that breast implants provide to patients. As a breast implant clinical trial investigator and the original medical director of Mentor's cohesive gel implant trial in 2001 to 2007, I also witnessed the challenges in the clinical studies.

I would submit to you, one of the greatest challenges to the current study designs is the required MRI. Aside from the patient expense, it can be, in some cases, fear of MRI. The literature suggests that MRI can produce a false positive rate of 10 to 20 percent of patients receiving them. These false positives frequently result in unnecessary operations for the patient.

We've seen these issues in the various breast implant clinical trials, but at the same time, issues are also being seen with approved SGBI 2006 labeling, where patients are recommended MRI at three years and then every other year postoperatively. This is especially in light of the confirmation that silicone gel breast implant rupture is not more than about one percent per year.

What I'd like to focus on today is why we are all here: to talk about the science and relative research and concepts, I am confident, can make future studies better for all parties, most importantly, our patients.

In 2009, ASERF sponsored a study comparing MRI to high-

resolution ultrasound in detecting implant shell failure. Many of you are familiar with this technology, as it is the standard for prenatal care. This study was performed by Dr. Brad Bengston and has been preliminarily accepted for publication. The highlights include benchtop studies proved that ultrasound technology is well suited for detecting shell rupture.

You can see in these slides here, this just demonstrates the high-resolution ultrasound showing an intact shell in the breast implant. This is a fifth generation cohesive gel implant, and you can see the disruption of the shell and its image on ultrasound. And then finally, this is a currently approved silicone gel breast implant with a small tear, and you can see again the ultrasound demonstrates that discount very readily.

The clinical arm of this study had 15 patients, 29 breasts with silicone gel breast implants, and it was prospectively followed. The group consisted of patients who were referred to the center after having an MRI suspecting rupture or other potential complications. All 29 breasts underwent a preoperative scan with the high-resolution ultrasound. All patients in the study group underwent surgical treatment where the findings of the MRI and ultrasound were confirmed. The results demonstrated that the high-resolution ultrasound was 100 percent accurate and similar to MRI in this cohort, with accurate identification of intact or failed implants in all patients.

The high-resolution ultrasound exam is in the office, it's

painless, and at a fraction of the cost and anxiety for our patients compared to MRI.

Based on this study, the authors and we at ASERF concluded that high-resolution ultrasound is a new horizon for best implant follow-up that benefits patients in many ways. This study is being expanded to enter 100 patients, but we believe this technology should be considered as an alternate replacement to MRI that have been so challenging for all of us.

Additional suggestions for new postapproval study designs include lifting the restriction on Betadine for breast implant irrigations, as we have ample evidence that this agent has reduced patient complications, specifically capsular contracture, as you've heard, the most common breast implant complication for the past 50 years and the most common complication and cause for reoperation in current gel implant core studies.

Betadine was restricted from breast implant contact in the year 2000 due to anecdotal concern that Betadine increased saline implant deflations. The basis was a small cluster of saline deflations from a single surgeon's practice where Betadine was actually being used to fill the implant.

We now have a large amount of robust data that demonstrates a reduction in capsular contracture using Betadine breast pocket irrigations that reduces bacteria and biofilm that we know cause capsular contracture. These data indicate that patient outcomes are improved with appropriate extraluminal Betadine irrigation, demonstrating a significant reduction in

capsular contracture with no evidence of any shell failure or increased rupture rates of saline or silicone breast implants. These results have been confirmed by multiple independent authors. The scientific basis for this requested labeling change is clear.

And, finally, simplified screening for postoperative patients. The greatest challenge is conducting compliant patient follow-ups. We know from my own 750 patients in FDA clinical trials that all breast implant patients that have any type of problem or issue or question come back on their own volition. We also know my patients who do not come back to follow-up visits are not having any problems and are doing well.

We are very confident that the screening of postoperative patients could be a combination of phone and e-mail follow-up with a three-question survey to identify a given patient, if a given patient requires additional follow-up. We believe this approach is more respectful of our patient's time and wishes and at the same time will easily identify patients who require a more comprehensive inpatient visit.

DR. LoCICERO: Can you sum up, please?

DR. ADAMS: I would like to gratefully thank the Panel for giving me the opportunity to speak today and commend you for your forward thinking on the postapproval study issue.

DR. LoCICERO: Thank you. Our next speaker is Lisa Swirsky. No Lisa Swirsky? Okay.

Next is Dr. Jean Silver-Isenstadt.

DR. SILVER-ISENSTADT: Good afternoon. My name is Dr. Jean Silver-Isenstadt, and I'm the executive director of the National Physicians Alliance, a nonprofit medical organization representing thousands of physicians across specialties and across the country. The NPA's mission is to promote active engagement of physicians with their communities to achieve high-quality, affordable healthcare for all and to promote professional integrity. The National Physicians Alliance refuses funding from pharmaceutical or medical device companies, and I have no financial conflict of interest to disclose.

I am not here today as an expert in the science of breast implants, nor in the clinical management of those who receive them. I'm here on behalf of the National Physicians Alliance to express our deep concern with the FDA's effectiveness in enforcing the rigorous completion of postmarket studies of these implants.

Regardless of medical specialty, physicians have to have faith in the assessments, approval criteria, and recommendations made by this critical agency. As front-line prescribers and as the first to be called when complications arise for patients, physicians depend on the FDA to set a high safety standard for device approval, to hold industry accountable when study obligations are not met, and to take substantive action to protect patient safety when data grows murky.

There is clear need for alarm when 71 to 72 percent of reconstruction patients and 80 to 81 percent of augmentation patients are lost to follow-up in the first three years of a mandatory 10-year study intended to establish long-term safety data, especially given the inherent conflict of interest in having the trials managed by those who stand to benefit financially from the procedure in question.

When the FDA's enforcement of postmarket study protocols is not robust, physicians begin to question the FDA's commitment to patients and to suspect undue industry influence. Research on pharmaceutical study results has shown that industry funded studies are 35 percent more likely to report positive outcomes than research funded by government. If industry bias is suspected in the case of MDA-mandated postmarket trials, this could result in physicians' hesitancy to support patients' participation in these studies, worsening the data collection challenge. It would also surely diminish patients' interest in completing the trials.

Similar concerns about bias also pertain to the surgeons who earn substantial income from providing breast implants. Are postmarket studies designed with adequate incentives for these physicians, including adequate staffing support, to maintain supportive contact with enrolled patients and to encourage the ongoing participation of these patients in the trials, particularly with patients who report complications?

From the consumer side, there are also understandable reasons

why patients might wish to avoid ongoing contact with physicians who they believe guided them into harm's way, or with physicians who respond skeptically when patients have questions about possible linkages between their implants and their symptoms.

What can be improved in the structure of these specific large postmarket trials to protect against these predictable human obstacles to long-term data collection?

And, finally, on a different note, how can studies limited to 10 years provide adequate safety predictors about slow-to-develop conditions such as cancer?

In sum, stronger incentives must be established for postmarket trial compliance in this instance, as well as in future trial design, including incentives for the physicians, for the companies, and for the patients, to ensure meaningful long-term data collection. The success of any new incentive structures introduced must also be carefully studied and followed.

If a formula for success cannot be found, the FDA should cease to approve drugs and devices based on promises of postmarket trials altogether, and should use its authority to rescind approval for devices of companies that fail to provide required safety data.

The National Physicians Alliance is heartened by this week's hearings and the FDA's attention to these issues as related to breast implants. We'd like to offer any help we might provide in supporting serious remedies

on this front. Thank you.

DR. LoCICERO: Thank you. Our next presenters are the Dorseys. Who's first? It's going to be Ms. Susan Dorsey first.

MS. DORSEY: My name is Susan Dorsey, I live in Mt. Juliet, Tennessee, and I'm here to share with you my experience as a participant in Allergan's trial for silicone breast implants.

When I turned 40 in 1995, I had saline breast implant surgery. I enjoyed these implants for 10 years and then, in 2005, I decided to have them replaced for cosmetic reasons. I met with Dr. Kevin Hagan at Vanderbilt, who recommended that I enroll in the silicone implant trial there. I paid my $6,000 and enrolled.

About a month post-surgery, while getting ready for a Christmas party, I remember having difficulty raising my arms over my head. Later in December, my family spent the holidays in the Caribbean. While there I experienced flu-like symptoms and spent most of my time in my room believing that I had swallowed some of the water or eaten food that wasn't agreeing with me.

January brought more new symptoms. The neck and shoulder pain that I had felt in December had worsened to the point that I was going to physical therapy three times a week. My vision began to become blurred, and I was experiencing a loud buzzing in my ears. Every day seemed to bring new health issues. These included severe joint pain, dizziness, anxiety,

tingling hands and feet, palpitations, insomnia, depth perception problems, loss of appetite, and a metallic taste in my mouth, many, many other symptoms as well.

Over the course of the next nine months, I had 24 doctors' appointments, including neurologists, orthopedic surgeons, and others. I had 31 physical therapy appointments, two MRIs, two spinal epidurals, and an admission into Vanderbilt's emergency room. In all, there were 63 medical appointments in the nine months following my joining that research trial.

Six months into the study, I felt close to death and called my daughter who was in college in Kentucky. I asked her to take care of my 12-year-old son if anything happened to me.

During the year before getting implants, I had only routine doctor's appointments, limited to annual physicals to monitor my thyroid problem.

Ten months into the study, I met with Dr. Hagan at Vanderbilt and advised him about the deterioration of my health since being in the study. I asked to have the silicone implants removed and replaced with the same saline implants that I had prior to being in the study. I was advised there was no exit strategy to leave the study, and that if I wanted the implants removed, I had to pay $3500 to have that done. He said he would throw in a free breast lift for my trouble and that he would contact Allergan and see if they would provide the saline implants for free. They would not,

and I ended up paying for that surgery. And on September 29th, 2006, my implants were removed.

During the time I was enrolled in the study, I had no contact from Vanderbilt or Allergan. I had called Allergan and left a phone message stating I had some health problems due to the research trial and requested a return call. I followed that with an e-mail, and I received no call or no e-mails, except for one that was a generic one saying that, due to FDA regulations, they could not comment on my medical conditions.

On April 16th, 2007, seven months after the silicone implants were removed from my body, I sent Allergan a certified letter advising that my medical problems were subsiding and that Vanderbilt's Dr. Hagan told me that the study implants had been returned to them for testing. I attached a copy of the device identification forms requesting that test results be mailed back to me. I've heard nothing. I would expect that very least from you.

I believe that most of this horrific period in my life could've been avoided had I been monitored during the time following my enrollment in the study. Not only was there no follow-up, but matters were made much worse when my requests for help were ignored. It was clear that no one was interested in hearing about my adverse reactions. What kind of research is that?

During my participation in this pseudo-research trial, I had over $100,000 in medical expenses, along with lost wages of over $400,000.

Fortunately, I had the mental and physical strength and the financial reserves to get through the past six years. I know of several other women who are not as fortunate. And I wonder if the kind of research conducted by Allergan would've identified or evaluated the kinds of serious health issues that I had with the silicone implants.

I was forced out of the study when I made the decision to remove the silicone implants in order to save my life. All records about my medical problems were deleted as though I never existed. Despite my repeated efforts, Allergan was not interested in learning about how their silicone implants harmed me or how my health improved when they were removed.

At the very least, the FDA must make sure that safety studies by implant companies should be conducted in an ethical manner. Problems should be reported, and injured participants should receive appropriate medical care. It is your job to make sure this situation changes immediately.

DR. LoCICERO: Thank you. Next is Mr. Pete Dorsey.

MR. DORSEY: Hi, how are you? I hope everybody's still awake. Please be advised that neither Susan, my wife, or I have been compensated by anyone for being here. We've done this on our own.

Susan and I have been together since 1999, and until she became a participant in the silicone breast implant study, she was extremely healthy. She was physically active, very competent, and a lot of fun to be

around. In 2005, almost immediately after she had her existing saline breast implants replaced with silicone implants, her health, her life, and my life began to change.

Not only would Susan describe to me the unusual things that she was feeling, but I could definitely notice some of the changes taking place in her. She started complaining of things like dizziness, very strong pains, physical and mental anxieties, blurred vision, and a host of other symptoms that were all new and that we did not understand the origin of at the time.

With these things happening to her, our lives changed. As things became worse, she became almost reclusive and our social lives became very limited. All kinds of doctors and medical visits became a necessary part of our lives. As the months went by, her health got noticeably worse. She reached the point that she couldn't even drive herself. I therefore had to somehow work into my job schedule the various trips she needed to make her many, many medical appointments.

In the years we spent together prior to the 2005 silicone implant replacement surgery, Susan was always very much in tune with her own body and the health of everyone in our family. She suddenly began to question her overall health and became suspicious of her new implants. Although unsure of exactly what was causing her new multiple health issues, she made the wise choice to have the new silicone breast implants removed from her body.

After removing these silicone implants and having them replaced with saline ones, her health immediately began to change for the good. Many of her symptoms and ailments started to disappear, and today, six years later, her good health has almost returned.

I am here today as a concerned husband in support of my wife, to tell you, as best I can in the time that I've been allotted, that my wife has needlessly suffered due to the silicone breast implants that were sold to her and surgically put into her body. As a family, we were forced to endure many trials and tribulations that should not have ever been. Not only can I advise you of the adverse changes that took place in my wife, Susan, and in our lives as husband and wife, but I can certainly also quantify the over $100,000 that she mentioned plus that we have had to spend because of this mess. All the studies in the world will not change anything for us.

In my opinion, these particular silicone implants should be totally banned from use and not be allowed to ruin anyone's life ever again. Thank you.

DR. LoCICERO: Thank you. Our next presenter is Dr. Suzanne Parisian.

MS. DORFMAN: Good afternoon. I am not Dr. Susan Parisian. She will be testifying tomorrow. Instead, I am testifying on behalf of a woman named Chelsea, who is not able to be here today.

DR. LoCICERO: I'm sorry, but you're out of order. We're going

to start taking questions now. I don't have you on my list.

MS. DORFMAN: I am replacing Dr. Suzanne Parisian for today.

DR. LoCICERO: No. We'll put you at the end of the line.

MS. DORFMAN: Okay, thank you.

DR. LoCICERO: Now let's go on to Cynthia Anne Mason.

MS. MASON: In 1998, I underwent bilateral mastectomies with Stage III construction. In 2000, I was going to have revision surgery. My surgeon was a principal investigator for the new clinical trial for silicone implants and recommended that I participate. He made multiple assurances that I could always have them removed if any issues arose. And the insurance company pre-certified the revision, and I became a part of the clinical trial.

The insurance claims were denied because the pre-certification had not revealed that the implants were part of an investigational study. My insurance coverage for reconstruction, as federally mandated, had been jeopardized by my participation in an FDA study. Later, when my COBRA was to expire, I was denied private health insurance because I was part of a clinical study.

Since my reconstruction with numerous issues, including -- I've had numerous issues, including lymphedema, extreme sensitivity to light and heat, and greatly exacerbated allergies, seroma, and capsular contracture. Most notably, in year one of the study, a seroma developed and I was told that it was just a bit of fluid that would probably resolve itself.

During the course of my participation, I went on numerous occasions because of the redness, swelling, and inflammation. At one point I was offered antihistamines and steroids to help alleviate some of my allergic response. As I realized that this drug therapy was geared towards covering up immune issues I was suffering from, from that point forward, I was treated with hostility, but I continued with follow-up visits. Many of my issues were better addressed by oral injectable antibiotics for several months by a different physician.

When I navigated an affordable way to be explanted by a different doctor, who's also four times board certified, at a different facility, I was abruptly told that only the implanting doctor could do the explantation.

In 2011, I saw the findings of FDA, which associated seromas with ALCL. This began my urgent quest to put an end to my problem.

In my research on the FDA website, I found that my serial numbers were not registered in adverse records. I then requested my records from the doctor. Despite dozens of visits, only two were ever recorded, and they ended with my desire to be explanted three years into the study. Today, as I speak, my seroma is in full blown, and I have never been able to navigate a way to be explanted.

James Baldwin once said that you cannot fix what you will not face. I'm here today because my experience in participating in a clinical trial is demonstrative of some of the current flaws inherent in patient informed

consent and the reporting of adverse effects.

Furthermore, I believe the investigational device exemption greatly diminishes accountability and motivation to derive the real information which might improve product safety or further innovation.

Finally, I implore that all of us be reminded of the principles of ethical research, of the Belmont Report, as well as the Hippocratic Oath, with respect for all participants by all clinical research.

Thank you for this opportunity to comment and express my concerns.

DR. LoCICERO: Thank you. We're going to take a break here and look at our -- start asking questions on this group of individuals.

Dr. Casas, it was unclear, from your presentation, if you are currently an investigator with these trials.

DR. CASAS: I am not.

DR. LoCICERO: Dr. Adams, can you give us the peer review paper that's published concerning this Betadine that you talked about?

DR. ADAMS: There's actually been quite a few publications. We published three, in 2000, 2001, and 2006, out UT Southwestern, there's been two papers out of Houston by Dr. Wiener, and there's been several publications out of Australia, Dr. Deva, D-e-v-a.

DR. LoCICERO: Does any of the Panel have questions concerning this issue? Yes.

MS. DUBLER: I wonder if Dr. Casas could return to the podium for a moment. Thank you. I have a few questions about -- you called yourself a physician and a patient advocate. And what percentage of your practice is devoted to breast augmentation?

DR. CASAS: Revenue or patients, because it's very different, you know?

MS. DUBLER: Okay.

DR. CASAS: I see a large number of patients, but operating on, you know, a different number. So in my practice, I see patients; I don't always operate on them.

MS. DUBLER: And when you see patients and women who come to you and would like breast augmentation -- and I'd like to keep the discussion to that -- how do you approach that first discussion with them?

DR. CASAS: It depends on their age and the reason for their visit. Is it pre-childbearing? Post-childbearing? Are they congenitally deformed with severe breast asymmetry? It completely depends on the motivation and the chief complaint.

MS. DUBLER: Okay. So I can see where a congenitally deformed woman would have a very particular set of reasons for wanting surgery. But let's say you take a 35-year-old woman who has three children and is beyond her, she thinks, childbearing desire and would like breast implants.

DR. CASAS: That particular patient, in my practice, typically has a deformity, a postpartum deformity of breast deflation. So they'd come to me with that feeling that I'm deformed. I used to have a full, you know, 34B, 34C breasts, and now I have no breast tissue at all, I just have skin, and they feel very deformed, and all they want is restoration of the pre-pregnancy breast size.

MS. DUBLER: Okay, now I'm pushing toward an ideal patient who is not deformed, who's finished having her kids, and who'd just like to be bigger.

DR. CASAS: I have very few patients like that because, you know, I have a very small select practice and I don't advertise, so patients that come to me fall into those categories. When they come to me with normal breast size and shape, I usually tell them that, you know, this might not be something to consider because you're electively putting a foreign body in you and you might want to think about the ramifications. So I don't really have a large patient population that comes for just augmentation with normal breasts.

MS. DUBLER: That's very interesting to me because I used to have a big advertisement on my office door that said, Do something nice for yourself today, get some new breasts. I rather liked that, and most of my visitors did too.

DR. CASAS: I think it's pretty tacky and unprofessional,

personally.

(Laughter.)

MS. DUBLER: I thought it was pretty tacky, too.

DR. CASAS: No, I don't advertise, though. But anyway, the majority of the patients --

MS. DUBLER: But lots of members of your profession do.

DR. CASAS: I don't monitor advertising by plastic surgeons, so I can't really tell you. I just can tell you what I do and how I've, you know, conducted my practice for 22 years.

MS. DUBLER: Thank you.

DR. CASAS: You're welcome.

DR. LoCICERO: Okay, we'd like to move on. We are having difficulty finding who this person is who wants to speak. We need your name and other information so we can place you at the end of the line today.

Yes.

MS. DUBLER: I wonder, were you planning to call Mrs. Dorsey back? She was in this last group.

DR. LoCICERO: You can certainly ask a question of Ms. Dorsey, yes.

MS. DUBLER: Yeah, Ms. Dorsey. Thank you very much. I'm very interested in what appears to be confusion about what the study is, who runs it, how do you get in it, and how do you get out of it? And it was mainly

your remarks that raised those issues for me. Tell me what you were told about how to get into the study.

MS. DORSEY: I was not looking to get into any research trial. I went into Vanderbilt's cosmetic surgery department, and the doctor that I met with informed me that I would be a candidate for the study and I asked if -- you know, I had heard over the years, you know, the bad press about the silicone, and I wasn't 100 percent satisfied, and he told me that he had been doing the silicone implants there for 30 years and he did not have one adverse reaction to those, which I learned later was not the truth. But based on that statement, I went ahead and got the silicone implants rather than going back with the saline implants that I had 10 years previously.

MS. DUBLER: The presentation, that getting the implant had this aura of being part of science, part of a study, was something that you felt was a positive, was a plus?

MS. DORSEY: That really was not my personal objective. I was told that the silicone was going to be more natural feeling, which it was not. There is a negligible difference between saline and silicone. That's just a lot of marketing hype, and that was not the case with me.

But no, it was the opportunity to get something new. It was supposed to be kind of like the Cadillac of implants at the time. And I was turning 50 and I fell for it.

MS. DUBLER: And so in this initial discussion about receiving

silicone breast implants, there wasn't a hint of this aura of uncertainty or there wasn't -- were you told that they had been approved by the FDA, pending larger studies, that that had been a condition of approval?

MS. DORSEY: I don't remember that. I don't remember.

MS. DUBLER: Thank you.

DR. LoCICERO: Dr. Leitch.

DR. LEITCH: Marilyn Leitch.

Ms. Dorsey, I had a question for you also, please. How did you find out that you were "deleted" from the study and all your data was deleted as if it didn't exist? How did you find that out?

MS. DORSEY: Well, I had written Dr. Hagan, who was the doctor that was in charge of the study, and asked him about my -- why I wasn't in there, and he told me that he was having his research nurse follow up to find out why. And that I suspected because I did file the FDA MedWatch and I don't think that I was ever -- well, first of all, I've never received any correspondence. I didn't get the FDA letter. I never got any request to come in for one-year follow-ups. I never had any correspondence with Allergan at all. So based on that and my -- and I did ask the doctor about that, why I wasn't there, and he just said he would have his nurse -- and I've sent two e-mails to them about what actually did happen to my records, and no one's ever gotten back to me.

DR. LoCICERO: Dr. Connor.

DR. CONNOR: So can you remind me of what year your surgery was?

MS. DORSEY: 2005.

DR. CONNOR: Okay. And do you know if you were in the core study versus the postapproval study?

MS. DORSEY: The adjunct study.

DR. CONNOR: Okay. And so since we get to ask Allergan questions, is it okay if we ask them a question about you later? Would you mind if we did that?

MS. DORSEY: Absolutely. Yeah, any time.

DR. CONNOR: Okay, thank you.

DR. LoCICERO: Dr. Mount.

DR. MOUNT: My question is also for the last speaker. When you receive feedback -- could you come back to the podium? Thank you very much. When you receive feedback -- the implants that were explanted from your body, did you get any feedback? Were they ruptured or not ruptured?

MS. DORSEY: I've tried for years to get that information from Allergan. I've sent them a certified letter, e-mails. I've sent them my -- each set of implants comes with ID numbers and serial numbers on them. I've included copies that came on the implants, you know, for my registration, and I've sent them the certified letter. I have no idea.

DR. MOUNT: Did you have an MRI before the explant?

MS. DORSEY: Yes, I did. I had a doctor that I knew personally that ordered one for me a night or two before I had the surgery, and it really wasn't -- the MRI machine that they had was in a small hospital, and it really was not the type that would've disclosed or shown any problems.

DR. LoCICERO: Okay, thank you. We're going to move on. I'm sorry, we need to -- we're starting to run behind here. Thank you very much.

Our next speaker is Cynthia Pearson. Cynthia Pearson.

MS. PEARSON: I'm Cynthia Pearson. I'm the executive director of the National Women's Health Network, which is an independent, not-for-profit women's health advocacy organization. We're supported by thousands of individuals across the country, and by choice. We don't accept funding from industry interests.

And kind of prophylactically, I'll answer the question you've been asking organizations about, whether they're partners of MedWatch. We are not an official partner of MedWatch, but we're strong supporters of it. And right now we're actually involved in an informal discussion group that the FDA has asked consumer organizations to give input into, dealing with some of the problems you've heard of, of the cumbersome form. So that's the context.

Over the 20 years that FDA advisory committees and panels have met about implants, I think I've attended every single meeting. I've spoken on behalf of the network. Our concern all along through this process

is that breast implants of all kinds be appropriated -- be regulated in a manner that's appropriate to the information that's known about their effectiveness, the short-term complications, and any possible long-term risks.

For many years the only appropriate regulation for implants was a moratorium because there had been no studies that supported an FDA ruling and assessment of their safety and effectiveness.

By the time types of that studies were done and submitted to the FDA, many, many questions had been raised based on case reports, case control studies, case series, anecdotal evidence that raised very troubling questions about possible long-term, serious, maybe rare complications.

By the time FDA issued the approval letters to Allergan and Mentor, their determination was, the only way those questions that had not yet been finally answered with an assessment of whether there was a true causal relationship, and if so, what the risk was, that the only way to answer those questions was with large, long-term prospective studies with comparison groups, studies that were powered to get answers about those specific questions. Because by this time, if they weren't answered, they were going to remain troubling, gnawing, and possibly real, but unable to inform anyone, in a really solid scientifically based way, what the risk was, so that women couldn't make a fully informed decision when it came to those conditions, unless these large, long-term, comparison-trial controlled studies were done. So here we are now. The studies have been launched, they're

fully enrolled, and the follow-up is terrible.

And on behalf of the National Women's Health Network, I want to speak to you Committee members who are guided by the Agency. You're asked to advise them on a list of questions that's been presented to you and is made available to us.

Question 1(b) says: Given the status of the current clinical postapproval studies, what changes, if any, do you think should be made in the current studies?

I'm very concerned that you're being asked a sort of vague question: What changes? Well, listening to the companies this morning, I think the companies would say drop that MRI part of the study. And they might even say accept low follow-up rates because it's just so hard, it's just such a hard topic. It's a hard population.

I want to urge you to, instead of answering that question in a way that says, well, let's just post hoc change the design of the study, change the endpoints, change the expectation, I want to urge you to advise the Agency to say this is unacceptable and your approval is revoked as of 12 months from today unless, by that time, follow-up has improved to greater than 80 percent.

Now, does that sound harsh? Yes, absolutely. It's a nightmare for the FDA to revoke approval. We know that. It's a nightmare for everyone involved. But the FDA needs to act in the interests of the public's health and

they've asked you to advise them.

So I want to say, is it harsh to revoke approval? Yes. Is it impossible to get better than 80-percent follow-up in large long-term trials of healthy women? No. No. We as a society have worked for 20 years to insist that women's health be taken seriously and that large numbers of women are enrolled in scientifically rigorous trials and they stayed enrolled. They stay in their follow-up.

The Women's Health Initiative, the study of women across the nation, multiple breast cancer prevention studies, the Nurses' Health Study, fracture prevention studies, heart attack prevention studies, all of them involving women who were healthy when they started, all of them involving thousands of women, some of them involving tens of thousands of women.

DR. LoCICERO: Please sum up.

MS. PEARSON: Pardon me?

DR. LoCICERO: Sum up, please.

MS. PEARSON: Okay. Are you using the same clock for me as everybody else?

DR. LoCICERO: Yes, ma'am.

MS. PEARSON: Okay then, I'll sum up.

Plenty of studies, it can be done, it needs to be done, it should be done, and I ask you, on behalf of the National Women's Health Network, when you get to Question 1(b) and you say what should be done about the

current clinical trials, you say that they should be -- the failure to perform them adequately, as promised, should result in the revocation of approval with a 12-month notice.

DR. LoCICERO: Thank you. Next is either Terry O'Neill or Jan Erickson. I'm sorry. Okay, sorry, I'm getting very confused. Thank you very much.

Dr. Gloria Duda.

DR. DUDA: Good afternoon. My name is Gloria Duda, and I'm a board-certified plastic surgeon, and I've been in private practice in McLean, Virginia since 1992. My practice includes both reconstructive and cosmetic patients, and I perform approximately 150 procedures per year that involve the use of breast implants in either primary reconstruction, augmentation, or revision breast surgery.

I am an investigator for the Allergan and Mentor breast implant studies, including adjunct, core, cohesive gel, and postapproval studies for silicone gel, and this has involved hundreds of patients which have been followed for 5 to 10 years post-implant in my practice. I have no conflicts of interest and no financial interest in industry or health professional societies, and as a board-certified plastic surgeon, I derive a portion of my income from surgical procedures using breast implants.

I am here today to discuss the importance of maintaining silicone gel breast implant availability to my patients, as well as keeping my

patients well informed about the long-term data regarding their implants.

Many of our patients who have had silicone gel implants for reconstruction or cosmetic purposes have returned for follow-up visits and feel that their procedure has had a positive impact on their lives, and if asked if they would make the same decision again, the response has been yes.

The current literature does support that the benefits of breast implants are both psychological and social, providing a sense of higher self-esteem, body image, and self-confidence.

In 2006, the FDA decided implants were safe and effective, and with the ease of access to information with today's media, the patients start with a consultation with a multitude of questions and ideas, and they come in with ideas that are accurate and inaccurate. As a physician, I must educate my patients with respect to the risks and benefits of the breast implants and the surgical procedure as well, so they can make an informed decision about breast surgery and the choice of implants. Access to information on the internet and television has also resulted in patients being more demanding and having a higher expectation for the results.

My patients who undergo breast reconstruction after mastectomy are looking for restoration of their body image and for ease in clothing and not dealing with external prostheses. The skin flaps are often thin, resulting in poor coverage for the implant, and silicone gel offers a more natural-appearing and less palpable implant with less rippling, resulting in a

more acceptable reconstructed breast for the patient.

My patients who undergo breast augmentation are looking for enhancement for improved proportions or to replace volume loss after pregnancy. These patients are often thin, they have thin breast skin, and have minimal breast tissue. As with the reconstructive patients, the silicone gel offers a more natural-appearing and less palpable implant with less rippling, resulting in a natural result and a satisfied patient.

In my practice, patients who underwent breast augmentation were all offered participation in the postapproval studies. Reasons patients declined were they were comfortable with their decision and information regarding their implants and chose not to participate in the investigative study; they did not want to commit to long-term follow-up.

The patients that are participating and have come in for follow-up appoints are satisfied with their results and do not want to undergo the MRI that we ask them to. They feel there is nothing wrong with their implants, they do not want to risk the false positive readings and undergo unnecessary surgery, and they don't want to undertake the extra cost of the MRI.

Many of my patients who have undergone breast reconstruction are undergoing MRI every two years for part of their breast cancer surveillance. And we do have access to this data, and this may be one way we can continue to collect the data regarding MRI changes with time and

age of implant.

As a plastic surgeon in private practice, my primary concern is conveying accurate information to my patients, and patient safety and satisfaction. I do have patients that have completed their 10-year follow-up in their studies and will be informed on how to guide these patients forward as they pass through the 10-year postoperative period.

I do appreciate the FDA's ongoing scientific review of the implant data, and I thank the Panel for this opportunity to speak. Thank you.

DR. LoCICERO: Thank you. Our next speaker is Mini Baylor Henry.

Okay, our next speaker is Dr. Mayman. I'm sorry, would you give your name, please, again?

DR. HAMAS: Yeah, my name gets killed a lot. I'm sorry.

My name is Robert S. Hamas, and I'm a plastic surgeon in private practice in Dallas, Texas, and I'm president of Ideal Implant, Incorporated.

Over my 32 years in private practice, I've used many different saline-filled and silicone gel-filled breast implants from various manufacturers. I personally experienced the difficulty of getting cosmetic breast implant patients back into my office for a follow-up visit and have observed how this limits data obtained in breast implant trials.

In 2006, I founded a company to develop an improved saline

breast implant that has an internal baffle to control movement of the saline so that it feels more like natural tissue.

FDA guidance for a saline implant requires a core clinical trial of 10 years, 2 years for the PMA submission and 8 years for postapproval studies. I wanted our trial to have better data follow-up than I had seen from other breast implant trials. So to accomplish this, a novel patient incentive program was devised, which I want to share with you here now.

For each of the 502 women that we enrolled in our trial, Ideal Implant deposited $3500 into an irrevocable trust fund. Spending almost $2 million on this was a huge investment for a small startup company, but it shows our commitment to get good data, and the follow-up has been excellent.

At the one-year follow-up visit, only 10 patients out of 502 were lost to follow-up. Most of those were because they moved out of the area of the investigator. The actual follow-up was 98 percent of expected follow-up. Remember, these are all cosmetic breast augmentation patients.

The terms of the participants' trust are quite simple. The $3500 for each woman is invested in a portfolio of stocks and bonds by the trust. The $3500 deposit is expected to grow to about $10,000 in 10 years based on historical market average returns.

When the last woman completes her 10-year visit, the trust fund will be closed and the funds distributed to those women who completed

all 12 of the required follow-up visits at 2 months, 6 months, and then yearly for 10 years.

If a woman misses any one visit, any of the required visits, she is exited from the trial and loses her share of the trust fund. However, her share remains in the fund to be distributed among the women who do complete all of the required follow-up visits. If a woman exits the trial, she receives $290 for each visit she did complete.

Each participant receives a monthly e-mail from the trust, listing their schedule of required follow-up visits and the current value of their share of the trust fund. So as of the end of July, each person's share was $4,534 per participant. We get e-mails from them when they change their address.

Note that women did not receive compensation for having the surgical procedure, where they were at high risk with a new device, only for follow-up visits, where they are very low risk. Thus, this strong financial incentive was felt acceptable to get the complete follow-up data on safety and efficacy that will benefit all those who may use this implant in the future.

In summary, this is a successful, easy-to-implement patient incentive program for obtaining high follow-up rates among cosmetic surgery patients. I want other sponsors to know that you're welcome to use a similar approach to improve the follow-up rates in the current silicone gel postmarket studies. Thank you.

DR. LoCICERO: Thank you. Now for our last speaker of the day. I still don't have your name.

MS. DORFMAN: Hi. Thank you very much for making this time available. I am testifying on behalf of a woman named Chelsea C. from Columbus, Ohio, who is not able to be here today.

"I was 38 years old in 2008 when I decided to get Mentor MemoryGel breast implants. I was the vice president of a successful $3 million special events company. I was in very good health, with only some typical allergies. I worked out at the gym three to five times a week, was very social in my community, and traveled frequently. I no longer have my fabulous job. I now work in a sales department trying to make ends meet. I struggle to work 20 to 25 hours a week, but desperately try so I can keep my health insurance, home, and my livelihood.

"I am in the Mentor study that you are discussing at this meeting. I want to explain to you why the study is not going to provide information about the terrible health problems that I had from my implants.

"I am 5'10" and have always been quite thin. I wanted to have some curves. I interviewed three doctors, had a baseline mammogram and passed my physical with flying colors. All three doctors told me the MemoryGel implants don't leak and showed me a photo of the implant cut in half. The doctors didn't discuss the possible health implications.

"I had my surgery in April 2008. I returned to work within five

days, but had complications almost immediately. I had intense burning on my right breast that turned fire red. My sternum swelled and bruised. After two months, I began getting one symptom after another. During the first year these symptoms included chronic canker sores in mouth, my hair falling out, my chest turning a deep red and burning when I was exposed to sunlight. I became irritable and moody. Scents overpowered me. I had insomnia. I gained weight, 15 pounds in four months. This was gaining weight. For the first time in my life, I had regular headaches and fatigue. I caught colds and flu frequently and couldn't shake them. My surgery incisions never properly healed.

"By the time I went to my implant doctor for my one-year follow-up, I lost about one-fourth of my hair. He said there is no way your hair loss is related to your implants. I believed him. I felt too intimidated to even ask about my other symptoms and didn't second-guess the implants for another year and a half.

"In year two, things got worse. I was having brain fog and dizzy spells. My right eye started burning sensations about twice week. My sleeping issues got worse. At this point I had to cut back my hours at work. My muscles would tire easily. By the end of the second year I had stopped going to the gym because I was simply too exhausted.

"My last year with implants was a living hell. I lost my boyfriend of four years, my position at work, friends, and my volunteer work.

I lost much of my income due to illness. I went from being active and productive to feeling ill and not being able to get out of bed.

"In November 2010, I hit rock bottom. My fatigue was so overwhelming I couldn't even go to the grocery store. I was waking up in the middle of the night with migraines. I couldn't cope with light and sound at the same time. I couldn't read. My legs and arms were in pain every minute, every day. I had tendonitis. I would forget very basic tasks. I had terrible joint pain in my wrists and ankles, fatigue, heart palpitations, a third of my hair was gone, and my eyes were bloodshot and painful. I had to get help.

"My primary care doctor wasn't sure what was causing this after running blood work. Sending me to get a CT scan, I went to visit an endocrinologist. I asked the endocrinologist what he thought about the implants and he said the only way to know is to get them out. And I believe his words saved my life.

"On December 28, 2010, I had my implants removed. My pathology report came back stating that I had microcysts containing refractive, unsustained material consistent with the silicone in my left breast. So the implants that wouldn't leak did, even though they weren't broken.

"Since surgery I've been trying to regain my health. Many of my symptoms have improved. I no longer have issues driving. My fatigue is less. My stomach issues are gone. Migraines are seldom. My hair is not falling out in clumps. My tendonitis is gone. I am much calmer.

"If my implant doctor would have even said my hair loss could possibly be from my implants, I would've had them removed after year one. Instead, I went around for an additional year and a half getting much sicker. I now wonder if I will ever completely recover.

"People trust their doctors to give them complete and accurate information. I don't feel I received this regarding my breast implants. I haven't heard from him or his office since my one-year checkup, and it took a month for me to get my medical records released from his office. I have contacted Mentor a couple of times, and they gave me my patient number in a voicemail.

"I do fill out my Mentor postmarket surveys annually and try to fill out the interim complication survey. But it's just that; it's a survey that asks me questions. It doesn't ask the right questions so that I can describe what happened to me. It does not ask about most of the issues or complications that I am having. It asks for a specific diagnosis. The doctors have not given me a diagnosis. All I have is a list of horrible symptoms.

"After over $25,000 in surgery costs and over $50,000 in lost wages, I am still trying to recover. I'm sorry I can't be at the meeting to tell you this in person.

"I am wondering whether those of you on the Panel who voted to approve silicone breast implants five years ago would be willing to admit that there are many patients, like me, who are being harmed by the implants.

I hope all of you will agree that research that has been done so far is not asking the right questions about the symptoms that so many of us are experiencing. If you can make sure that the right studies are done and make sure that the doctors and patients across the country are aware of the risks of breast implants, I hope you can prevent other women from going through the hell that I have been going through.

"Thank you for your time."

DR. LoCICERO: Thank you. Now we'll ask questions of this last cohort, the first one to Dr. Hamas.

Which was longer, the informed consent discussion or the financial disclosure?

DR. HAMAS: The IRB put the financial disclosure in the informed consent, and it's about a page. You know, there's a few more bullet points that I went through just because of time limitation, but that was actually part of the informed consent, and the IRB was very helpful in the wording and so forth, of exactly how that would be. It's on our website if someone would like to see the details.

DR. LoCICERO: Dr. Connor first.

DR. CONNOR: To you. It seems that Mrs. Dorsey believes -- and I don't know if this is true or not -- that when she was explanted, she ceased to become part of the study. Do you feel that your patients may fear that, let's say, they're explanted --

DR. HAMAS: Excuse me for interrupting, but I'm not part of the study --

DR. CONNOR: No, no, I understand. So I'm saying, but that's, you know, one condition and, you know, that one patient is having in one study. So I'm asking, a patient in your study, let's say --

DR. HAMAS: Yes, sir.

DR. CONNOR: -- a patient needs to be explanted. Do you fear that she may erroneously believe that if her implant is taken out, that she would cease to be part of your study? And most studies would want you to be continued to be tracked. Is that clear so a patient doesn't --

DR. HAMAS: Yes, it's very clear that if they have the implants removed and not replaced with another manufacturer's implants, they remain in the study and thereby in the trust fund. They have to come in for their follow-ups. And this was actually one of the FDA requirements when we had our IDE approved.

On the other hand, if they choose to have our implant removed and, say, replaced with another manufacturer's implant, just like the current trials, they're no longer in our trial. And then they're paid the consolation, if you will, which was $290 per visit completed. And where that number came from, the IRB said, well, you put $3500 in and divided it by 12, that's $290 apiece.

DR. CONNOR: And that seems to be a big incentive, though. If

at 8 years and we hear that, you know, that the median time of this may be around 10 years, that if someone needs to be explanted and wants to try something else, you know, that they may be incentivized to get that $10,000 and stay in longer, though. I think it's a great study design.

DR. HAMAS: Thank you.

DR. CONNOR: And it seems to be where incentive is bordering on, you know, maybe the patient is not doing what she would normally do in her best interest.

DR. HAMAS: Well, I think what would balance that would be to remember that case report forms -- also one of the criteria of the trial is to assess efficacy and patient satisfaction. So if a patient was expressing definite satisfaction, then you wouldn't think that they were staying in the trial to get the long-term follow-up.

DR. CONNOR: Is this a premarket approval study that you're doing?

DR. HAMAS: Oh, yes, sir, this is a core study.

DR. CONNOR: So what if your thing isn't available in eight years when she's -- you know, the deal is you have to get your device again or no device. What if it's not --

DR. HAMAS: God help me.

(Laughter.)

DR. LoCICERO: Dr. Mount.

DR. MOUNT: My question is also for Dr. Hamas. What is involved in these follow-up visits? Do the patients, when they return for your study, which has an excellent return rate, do they require an MRI for each visit?

DR. HAMAS: No, our follow-up visit in our trial is pretty much the same paperwork as the Allergan and Mentor saline and gel trials, with, of course, the exception of the MRIs. But there are physician visits, questionnaires, patient satisfaction questionnaires, physical examination and evaluation by the doctor. Just pretty much the forms look very, very similar.

DR. LoCICERO: Dr. Vega.

DR. VEGA: I think you have given a new meaning to put your money where your mouth is. May I say that it's put your money where your breast is?

DR. HAMAS: Yeah.

DR. VEGA: May I ask you a question? It seems to me that you are rather involved with your patients. I'm saying that in a positive way. And I'm wondering if your staff has training and if in fact it's not just come in to check out, but it has some kind of an interpersonal kind of relationship.

DR. HAMAS: No, this is a nationwide trial. There are 45 plastic surgeons at 35 sites nationwide, so it isn't me. This is just the patients and their doctors that are coming in.

DR. VEGA: You're actually referring to a way that -- is there a

staff training? Is there some kind of -- this sounds somewhat different than the past two presentations, or is it that you're just suggesting it that way and it's coming out different?

DR. HAMAS: No, I think the training that the sites had and their study coordinators would be very, very standard and similar to any of the other trials. Again, we had the benefit of seeing trials before and could learn from them. It's always easier to improve something when you've seen someone else's work. So it was easy for me to look at it as we were designing the trial and saying, well, we can make these improvements. But the training and what they had, there was nothing special about follow-ups.

DR. VEGA: Well, let me ask, would you be open to having trainings for your staff that might be not only hopefully sensitive but also helpful to keeping patients available?

DR. HAMAS: Of course. I mean, as you see, I'm driven by getting really good data. I mean, I had a personal goal, that I would get the best data we could possibly ever get, and that's what I'm trying to achieve.

DR. LoCICERO: Okay, Ms. Dubler.

DR. VEGA: It's about the market. How are you doing? The stock market's not doing too well.

DR. LoCICERO: That's really not -- we're getting off the subject.

(Laughter.)

MS. DUBLER: I have two questions for you, please.

DR. HAMAS: Okay, sure.

MS. DUBLER: One is, do you advertise the availability of this new implant?

DR. HAMAS: Oh, no, the implant is in a core study. We only did very limited promotional things to get people enrolled in the trial. I mean, once enrollment was completed, which has been -- let's see, enrollment was completed February, a little over a year ago, so about 18 months.

MS. DUBLER: What were the promotional things that you did?

DR. HAMAS: These were just IRB things and notifying people that there's a new breast implant on the market, some of the design features, the technology of what we were trying to achieve with it, that it was saline, that it didn't have some of the limitations of silicone gel implants, they were not being paid to have their surgery. I'm trying to remember the wording in it. I'll be happy to forward you a copy.

MS. DUBLER: And given that, what are the incentives for the surgeons who choose to suggest your implant rather than those "approved" as safe and effective in the market?

DR. HAMAS: The way the trial was structured was that the surgeons essentially, that we exchanged dollars, got the implants for free. The patients paid for their surgery. And then the surgeons are paid $100 for each follow-up, each of the required follow-up visits, so two months, six months, one year, and so forth.

MS. DUBLER: So let me be clear. The implant is for free. And what does a silicone gel implant cost if a surgeon were not going to use your free one?

DR. HAMAS: Again, for the purposes of the trial, we priced the price of the current saline implant, which is about $500 a pair, rather than the current silicone gel, which is about $1500 a pair. So what we did is we charged the doctor $500 for the implant, and then when enrollment and all the paperwork was properly done and finished, then he got the $500 back.

MS. DUBLER: And do you have any sense -- I mean, I'm assuming, perhaps erroneously, that these surgeons are using your experimental saline design implant while they are still using other saline and silicone gel implants.

DR. HAMAS: Oh, yes. I know that during the enrollment period, the investigators, as part of informed consent and giving patients all options, showed them all three implants and, you know, they showed them the current single-lumen standard saline implant, the silicone gel by whatever company they were getting implants from, and ours as a third option. There was no restriction. They could do whatever they normally did in their practice.

MS. DUBLER: What I'm searching for is bias in your data because I don't think that a woman comes in and looks at these three alternatives and flips a coin. So I think that there is something in the

interaction between the woman and her surgeon that determines whether or not she will choose your new design, and it is in that choice that I think bias will be reflected.

DR. LoCICERO: We'll discuss that in more depth when we get into the questions.

One last question from Dr. Jones.

DR. JONES: This is a question about the follow-up, the yearly follow-up that is done in the plastic surgeon's office. What typically takes place and why is it do you think that most people -- we've talked about that -- they move around and so forth? Does it require the expertise of the plastic surgeon for that follow-up, or can that be handed off to someone else? If they go to a GYN appointment or some other -- receive some other medical care, is that the kind of thing that could be followed up in another way, so at least you get some kind of follow-up in the patients?

DR. HAMAS: As a practicing plastic surgeon, I really feel that a plastic surgeon is best qualified to do follow-up on a breast implant trial. I truly think they would pick up subtleties that an OBGYN might not, you know. So I think that would be -- because we are not in business and we don't have doctors around the country that could do follow-up in case a woman moved, one of the things we asked in the trial was that patients live within 100 miles of the investigator to try and at least get him started off nearby. Now, as I said, some have moved away, and we had one even move out of the country.

But we don't have anybody, say, in New York City to see a patient. So sometimes we've lost a couple like that.

DR. LoCICERO: Okay, Dr. McGrath has a burning question before we conclude.

DR. McGRATH: Yes, I had two very brief arms on a question. One is for Dr. Duda, who had spoken before, who's a practicing plastic surgeon. And, Dr. Duda, you mentioned about the reluctance of people to get MRIs.

Could you tell us what your patients in the two groups -- it sounds like you're involved with both reconstruction and augmentation -- what your percentage of return is and what you think the problem is and what you think you could do to make it any better?

DR. DUDA: Between the reconstructive group and the augment group, most of my patients in trials are in the reconstruction, so I probably have 70 percent reconstruction and about 30 percent augmentation, and those that are in the augmentation side are in the postapproval studies.

We have very good compliance with follow-up MRI for breast reconstruction patients that come back, and I just feel that patient population who has been ill with breast cancer is accustomed to making time in their busy schedules to come back for their follow-up visits with their oncologist, with their breast surgeon, and also with their plastic surgeon.

The augmentation patients who we've called back and our

compliance rate, you know, just for postop visits is very low, and the patients do make their appointments, but then they cancel. And we do communicate with them. They feel that they have no problems, verbally, over the phone, but to get them into the office, they've got busy schedules. In this urban area, patients are very busy. They're busy moms, they're busy working. To get them in, it's difficult.

And regarding the MRI issue for the augmentation patient, I think the biggest thing is the cost, and they feel they have no problems. For the reconstruction patients, we have almost 100 percent MRI compliance.

DR. LoCICERO: Okay, thank you very much.

This concludes the Open Public Hearing session for today. We're going to get to do this again tomorrow. I do want to give a little bit about the questions that I was asking.

The majority of women who were presented who had issues, a majority of them did participate in the trial or reported to the FDA. Probably around 60 percent. Of the organizations that belong to the FDA MedWatch partner program, the ASAPS is a member. There are a number of other surgical organizations that are members. Many nursing organizations are members. The only consumer group that might have interest in this particular issue is not represented today, and that's Lamaze.

So it's now time for a short break. We're only running a half-hour behind, believe it or not. Let's take a short 15-minute break and be back

at 4:20. Thank you.

(Off the record.)

(On the record.)

DR. LoCICERO: Thank you for returning. We are now going to have a presentation by the FDA on methodological issues.

DR. TOPALOGLU: Good afternoon, distinguished members of the Panel and members of the audience. My name is Ozlem Topaloglu, and I am an epidemiologist at the Division of Epidemiology, Office of Surveillance and Biometrics. I will be presenting methodological issues in future postapproval studies for silicone gel-filled breast implants.

Here's the outline of my presentation today. First, I will talk about endpoints for safety and effectiveness in the postapproval studies for silicone breast implants. Then I will discuss study designs for these postapproval studies and challenges regarding the study designs. And, finally, I will talk about possible data sources that can be utilized to address postmarket questions for the long-term safety and effectiveness of silicone breast implants.

Currently there have been three endpoints studied to evaluate long-term effectiveness of breast implants. The first one is circumferential chest size change and bra cup size change, which is usually used for augmentation patients.

The second one is the patient satisfaction. This endpoint is

assessed by asking patients questions about their satisfaction with the shape, feel, and size of the implants and whether the patient would have the initial surgery again.

And the third endpoint is the quality of life. This endpoint is typically assessed by questionnaires that measure several domains, such as self-esteem, body image, and general health outcomes. Some of the instruments, some of the examples of instruments, are Breast-Q, Rosenberg Self-Esteem, Body Esteem Scale, Tennessee Self-Concept Scale, SF-36, and Functional Living Index of Cancer.

The Panel will be asked whether it is necessary to measure long-term effectiveness and, if so, the optimal methods to measure it.

In the postapproval studies, there have been mainly two safety endpoints evaluated. The first one is local complications and adverse outcomes. These include capsular contracture, reoperation, implant removal, implant rupture, wrinkling, asymmetry, scarring, pain, and infection.

The second safety endpoint is rare complications for which causality has not been established. These include connective tissue diseases, cancer, neurological diseases, reproductive and lactation problems, and suicide or attempted suicide.

The Panel will be asked to discuss the safety endpoints that should be assessed for how long and how often safety should be assessed and whether this varies by endpoint, and the optimal method for collecting safety

data.

We have identified several methodological issues for safety and effectiveness endpoints in postapproval studies for silicone breast implants. These are: the optimal methods to measure effectiveness, safety endpoints that need to be addressed, the length and frequency of assessments for endpoints for safety and effectiveness, and thresholds for determining or interpreting safety and effectiveness results.

Next, I would like to talk about current study designs and challenges of these designs for breast implant postapproval studies. First, I will discuss new prospective cohort studies, which were referred as large postapproval studies in the previous presentations.

New prospective cohort studies enroll new patients as part of postapproval studies, and these patients are followed for a long period of time. These studies are conducted to study local complications and adverse outcomes such as, as previously mentioned, implant rupture, local complications. In addition, these studies are designed to capture less common and rare outcomes such as CTDs, cancer, neurological diseases, lactation and reproductive problems, and suicide or attempted suicide.

I will focus on two challenges regarding this study design: (1) sample size issues due to the safety endpoint we might choose to evaluate, and (2) the type of comparison group.

If the new prospective cohort study is powered on less

common diseases such as rheumatoid arthritis with an estimated incidence of less than 50 cases per 100,000 persons, the required sample size would be 2,800 participants.

The sample size calculation includes an adjustment for a 35 percent loss to follow-up over 10 years; assumes 80 percent power to detect a doubling in the baseline rate derived from national norms; and the one-sided significance level of 0.05.

On the other hand, if the new prospective cohort study is powered on rare disease outcomes such as scleroderma, with an estimated incidence rate of 2.85 per 100,000 person-years, the required sample size would be approximately 40,000 participants.

Similarly, the sample size calculation includes an adjustment for a 35 percent loss to follow-up over 10 years; assumes 80 percent power to detect a doubling in the baseline rate derived from national norms; and the one-sided significance level of 0.05.

The second challenge we identified in the new prospective cohort studies is the type of comparison groups. These comparison groups include saline breast implant patients; women undergoing other aesthetic surgery such as autologous fat grafting; national norms and population-based disease rates, such as surveillance epidemiology and end results; disease rate estimates from other registries; and reference study populations in the literature known as historical control groups.

In order to detect local complication rates at least twice as high in silicone-filled breast implant subjects than in saline-filled breast implant subjects, the required sample size would be approximately 15,000 control patients. This sample size calculation is based on the events with incidence rates of at least 1.2 per 10,000 person years; includes an adjustment for 35 percent loss to follow-up over 10 years; 80 percent power for a one-sided test at the 0.05 significance level; and it assumes a sample size of 40,000 silicone gel-filled patients in the treatment arm for comparison.

A new enrollment study could be supplemented by an alternative study where new prospective cohort studies can focus on capturing less common diseases and local complications while alternative study can be designed to capture rare disease outcomes.

An example for such an alternative study is a case control study. In this case, a case control study can be designed to include a patient population with a rare disease outcome of interest such as rare CTDs like scleroderma or systemic lupus.

In such a case control study, in order to address that there is no association between the rare outcome and presence of breast implant, 1,500 cases and 4,000 controls would be required. The sample size calculation is based on a 1 percent prevalence of the breast implant in the afflicted population with 80 percent power to detect a relative risk of 2 and the significance level of 0.05.

We have identified several methodological issues regarding study designs for new prospective cohort studies. These are study questions that need to be addressed; study design; safety and effectiveness endpoints that need to be assessed; comparison group; inclusion of specific patient population; and duration of the follow-up period.

The Panel will be asked to discuss study designs for future postapproval studies for long-term postmarket safety and effectiveness of silicone gel breast implants.

Data sources to evaluate long-term safety and effectiveness of silicone breast implants are primary data, registries, administrative health databases, and medical records.

Primary data can be obtained from studies that are designed to collect long-term data on women with silicone breast implant regarding safety and effectiveness.

Another data source is registries. Registries can be valuable tools for evaluating safety of silicone breast implants in routine practice. They may provide long-term data on local complications and rare adverse events.

Some examples for breast implant registries are Canadian CBI Cohort, Danish Breast Implant Registry, International Breast Implant Registry, North American Breast Implant Registry, Swedish Breast Implant Registry, and U.S. Augmentation Mammoplasty Cohort.

However, registries have a number of limitations such as quality of data; lack of control cohort; potential source of bias; voluntary nature of most registries regarding enrollment and reporting; and challenges in the analysis and interpretation of the data.

Another source of data that can be used to address some of the postmarket questions regarding silicone breast implants is administrative health databases. Administrative health databases may provide existing source of longitudinal information on women who have silicone breast implants. Some examples of administrative health databases are from countries especially with single-payer government health insurance systems, such as most European countries, Canada, and Brazil.

However, there are several limitations of using administrative health databases. These are quality of data; breadth of information collected; potential sources of bias. When data sources outside the U.S. are used, variations in demographics, care practices, and healthcare resources may limit the generalizability to the U.S. population. Additionally, lack of unique device identification may also limit findings since conclusions can only be drawn on the device classes such as silicone implants or saline implants; however, the specific model or brand cannot be determined.

And, finally, medical records can be reviewed to assess the outcome of interests, such as less common diseases or rare diseases.

Some of the limitations of medical records are: they are not

designed to study the outcome of interest and the data is not collected systematically.

Bayesian methods may be useful to synthesize data on breast implants from various sources using methods such as hierarchical models. These methods can be used to combine multiple studies such as core study, continued access studies, and new prospective cohort studies. As a result, statistically more power conclusions can be made.

In addition, Bayesian methods can be used to synthesize data across breast implant manufacturers for endpoints that are not specific to a particular brand.

The Panel will be asked to discuss the other data sources outside of primary data that could be used, and use of Bayesian methods to synthesize data from various sources to evaluate the long-term safety and effectiveness of silicone breast implants in the postmarket setting.

And this concludes my presentation this afternoon.

DR. LoCICERO: Thank you.

Does the Panel have any questions for the FDA? We'll begin with Dr. Glassman.

DR. GLASSMAN: Len Glassman.

One question. In the middle of the presentation, you talked about the assumption of a 35 percent loss of patients over a 10-year period. How do you justify that number, given what we heard this morning from the

two manufacturers about their real-world experience that was much, much higher than that in terms of patient loss?

DR. TOPALOGLU: That was our target, goal, and both sponsors agreed on meeting those goals. And well, they need to work on it, I guess.

DR. LoCICERO: Dr. Connor.

DR. CONNOR: Can we go to Slide 61, for example, here?

So, you know, it seems like there's a big open question regarding these, sort of proving they're safe, which is a hard thing to do.

Sixty-one.

DR. TOPALOGLU: Sixty-one.

DR. CONNOR: And so this looks like a study design where we would want to prove those rates are different, not prove those rates are the same, meaning, you know, I would expect to see something here like a non-inferiority study or a study against some sort of objective performance criteria.

For instance, in CDER right now, if you want a hypertension drug approved, you essentially have to prove that it's heart-safe and there's new guidance on that. And you have to show, for instance, that the upper bound of a confidence interval is less than 2, not that that confidence interval isn't not bigger than 1, which is very different and especially in light of huge loss to follow-up.

In fact, if we see huge loss to follow-up and companies throw

themselves on the mercy of the Panel and say well, it's really, really hard, then running a bad study is in their benefit because they're going to lack power; whereas if you make them do a non-inferiority study, the onus is on them to get the sample size and get the follow-up and get the numbers that will lead to a well-powered non-inferiority trial.

So I guess I'm wondering why this looks like a superiority trial and not a non-inferiority trial.

DR. TOPALOGLU: Need to defer that to our statisticians.

MS. SILVERMAN: Phyllis Silverman, CDRH.

It's really neither a non-inferiority or a superiority trial. Remember, we don't have a control group that we're really comparing to. What we're looking for is an increase in adverse -- it's a safety study.

We're looking for an increase in adverse events rates, and what we thought was clinically meaningful was a twofold increase or a relative risk of two, and that's how the studies are powered. It has nothing to do with non-inferiority/superiority; it's just putting the confidence interval around our estimate of the relative risks and being assured that if it's a twofold increase, that it will detect it.

DR. CONNOR: Right. And I guess my concern here is if the truth is that it's twofold and we run studies that seem -- are feasible, not studies that perhaps aren't feasible or at least companies aren't willing, in the real world, to perform, and that's maybe what we're observing, is that, you

know, this won't be statistically significant and it sounds like a non-statistically significant result; it's proof of safety and that's -- we don't believe that.

So it's on the CDER side right now. You're making companies show, for hypertension, that that confidence interval is less than 2, which is different than this study, saying if the confidence interval is not more than 1, it's safe, versus saying if it is less than 2, it's safe.

MS. SILVERMAN: Well, this is postmarket, first of all, and we decided that if the relative risk was not elevated more than twofold, that that was essentially negligible; it was considered comparable.

DR. CONNOR: Yeah. And I guess my concern is that the confidence interval can be so huge here that it's -- you know, it's going to span 2, but it's going to span 1 and it's going to include -- you know, my concern is it's going to be so broad, we don't know, and that's the case. We're running really large 40,000-patient studies that tell us nothing because the companies aren't incentivized to get the answer that we really care about.

DR. KRULEWITCH: Okay, this is Cara Krulewitch

Just to add on to that, we're presenting this as an example. This is for postmarket studies where a reasonable assurance of safety and effectiveness has been established prior to approval.

And I encourage you to hold on to those thoughts when we get

into the discussion because that's why we put this up here for discussion purposes because you're raising very valid concerns. And I appreciate them.

DR. LoCICERO: Other questions? Yes, Ms. Dubler.

MS. DUBLER: I don't have the technical ability to put this question as carefully as Dr. Connor did, but at one point in the slides it says that we assume that the complication rate from silicone gel implants is twice as high as from saline. Do you recall that slide? I don't know which slide it was. I don't have a number.

DR. LoCICERO: It's in parentheses.

MS. DUBLER: Sixty-three. Could you try -- someone said 63.

DR. KRULEWITCH: I don't see -- and 63, does it say "design" on it? Yeah, your numbering may be a little different. There it is.

MS. DUBLER: Could you -- to detect local complication, can you explain this slide to me? Does this slide mean that we know there are higher complication rates with silicone-filled breast implants than with saline?

DR. KRULEWITCH: No, no.

MS. DUBLER: Then explain to me what this slide --

DR. KRULEWITCH: This is a hypothetical, as is the other slide, where we're taking an example because we are looking at the -- our treatment group, per se, is the silicone gel-filled breast implants, and we're using saline controls as a comparison group.

So we're saying -- we're making an assumption, hypothetically,

of a twofold difference between the two groups because we're monitoring the safety in the SGBIs. And if it were that, it would require 15,000 patients.

This example is more to make a hypothetical presentation for -- and using certain assumptions so that we can give you an approximate sample size. That's all the purpose of this slide is. It is not suggesting that there's a twofold difference; it's not suggesting anything about the science or what we know. It is just a hypothetical example.

MS. DUBLER: Then I have two other follow-up questions, again for people who aren't statistically sophisticated. Forgive me.

In many of the slides, it talks about the power to detect rare diseases, and yet the testimony that we heard today was not about rare diseases; it was about generalized miserable lives. Now, the women who spoke seem to think that once they had the silicone gel implant taken out, they were no longer in the studies. Is that your understanding?

DR. KRULEWITCH: I don't understand what you mean by "our understanding."

MS. DUBLER: Is that the FDA's understanding of the design of the two studies?

DR. CONNOR: I think the concern is that what is being measured here, like, you know, rheumatoid arthritis and things like that, things we're hearing. "I felt awful, but I didn't have a diagnosis."

MS. DUBLER: Right.

DR. CONNOR: But FDA cares about "this makes me feel awful and miserable, and I wish I never would've had this done."

DR. KRULEWITCH: It went off again.

Yes, FDA does care about that. And I think those are things to save for the discussion that we're going to have with the questions, as to what are the outcomes that we want to measure. That is one of the questions we're going to be asking you. So you're asking a good question.

MS. DUBLER: But I still don't understand whether it is your understanding, at the FDA, that once the implant is taken out, the woman is no longer in the study. Is that how you, at the FDA, understand these studies?

DR. KRULEWITCH: The protocol, as far as I understand, is that even if implants are taken out, women are still being monitored and followed for the 10 years and the data is being collected on them and questions are being asked of them throughout the life of their enrollment in the study.

Is that -- okay, that answered your question.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: With regard to actual study design, if you go to your data sources, you know, you listed four data sources: the primary data, the registries, databases, and medical records. And I guess I would ask you, I think, at this point, you still think that primary data is the most powerful of these? You've listed the pros and cons of each, but you still think that

primary data is the one that's the most useful, to be gathering to try to get to the endpoints we want? Is that -- am I correct on that?

DR. KRULEWITCH: I think that will be a good discussion question. Clearly, in any study, the gold standard of studies is a randomized, controlled clinical trial. In the postmarket setting, we work in observational studies most often because those studies are, number one, too hard to design and, also, they don't really reflect the real world.

So do we think it's the most powerful? Perhaps. But is it the best study for these particular devices and the best way to monitor them? That's why we're here today, to ask you those questions.

DR. McGRATH: In the postmarket world, do you think that there is a difference that shows up, that's different from the more regulated cohort studies that you need to have for core studies?

DR. KRULEWITCH: I think that would vary from design to design of the studies that you would see pre-market. It could. And that's something I think we want to hear from you, as well, in your expertise and experience.

DR. LoCICERO: Dr. Connor has another question.

DR. CONNOR: So this is a question, I think, to help guide us or at least guide me.

So in, for instance, Mentor's core study, they had 15 percent follow-up through eight years, and in their postapproval study, they had, you know, an embarrassing 21 percent through one year, and we know why,

because they had a huge incentive to get good follow-up in the core study, approval, so they could sell their device. They have very little incentive in a postapproval study.

So I guess my question is sort of legal and to FDA is, what is their true incentive? Like, has FDA ever said your postapproval study is so awful, we're removing your product from market? You know, what is their honest-to-God incentive to do this well, because that's important to us is, when we recommend to you how they should be doing this the rest of the way.

DR. MARINAC-DABIC: Maybe I'll take that question.

You know, from the studies, from my presentation this morning, you saw that the huge -- and the vast majority of the postapproval studies are progressing well. We have -- so you saw that we have 19 percent, between 19 and 20 percent of the studies that are not progressing well.

So that speaks to the philosophy and to the actual willingness of the companies to really do due diligence in terms of making sure that not only the FDA, but the companies and the clinical community and the patients really get the best knowledge.

If you ask me about have we ever removed the PMA approval from the market, no, we have not. Does it mean that we -- if you ask me if we do have this authority, the answer is yes. So I think, you know, as the Panel deliberates today and tomorrow, I think you need to keep all the

options open.

I think the purpose of the FDA target was given in the afternoon. It's really to illustrate the possible options that we can use to answer the questions, meaning that there can be, you know, continuation of the current study design. It can be combination of different study designs. It can be different data sources supplementing the information, creating the national registries that can encompass, you know, the patients of all breast implants, produced by all manufacturers.

So these are the type of things that I'd like you to think about and hopefully, you know, utilize some of the framework that they presented this morning where FDA is going toward, you know, fostering the development of registries, fostering the partnerships, having -- stakeholder input, meaning that we need to focus on essentially expanding the infrastructure, building the infrastructure that will stay and not to be dependent only on postmarket requirements that are going to be closed as soon as the particular requirement is met.

So I guess in that spirit, I'd like you to be open-minded and interpret the presentations that were given by the FDA as our really strong willingness to change the course, the way how these studies are designed, relying on your expertise on what can be done in the future to make sure that we take advantage of assimilated sources, of innovative methods, and certainly making sure that the patients get the best information available.

DR. LoCICERO: Dr. Honein.

DR. HONEIN: Yes. Is there information available on the total population being implanted each year in terms of demographics, age, race, any variables such that we could evaluate these various data sources and how representative they might be of the population being implanted overall?

DR. KRULEWITCH: I believe that's in your Executive Summary. I can double-check. But there is information, and if it's not in your Executive Summary, it is in the white paper that was also included in the Panel Pack that you have.

DR. HONEIN: For the 380,000 implants a year?

DR. KRULEWITCH: No, for those that were within the study.

DR. HONEIN: No. So I'm asking about all the implants.

DR. KRULEWITCH: And I think that was asked earlier, and I don't --

DR. HONEIN: Okay.

DR. KRULEWITCH: -- know that we got that answered from Mentor and Allergan. We don't have that data, per se. That's one of those challenges that we don't have, the full denominators of data of all people who are implanted with devices.

DR. HONEIN: Because looking at things like the percentage of African-Americans that are enrolled in the study, it's difficult for me to evaluate --

DR. KRULEWITCH: Yes, yes.

DR. HONEIN: -- how good that is without having any sense of what part of the population they represent that is implanted. I know what part of the population they are, but --

DR. KRULEWITCH: I understand.

DR. HONEIN: -- I don't know how implants vary.

DR. KRULEWITCH: We can work to try and get that information for tomorrow.

DR. HONEIN: That would be excellent, thanks.

DR. LoCICERO: Thank you.

Okay, Dr. Leitch.

DR. LEITCH: So, you know, we're looking at these data sources, different ways to do a study. I'm wondering to what extent the FDA regulates or oversees the postmarket approval studies once they're "approved" with respect to issues such as data, safety, and monitoring committee, you know, the identification of patient data, methodology of follow-up, because some of the things we -- you know.

And, again, we don't have it to know for sure, but some of the things we heard from people who said they were participating in the clinical trials doesn't sound like exactly what goes on in clinical trials I know about, so does FDA have any purview with respect to that? Because we can do all these different ways of doing studies, but if a study design isn't being

implemented properly, then you know, it doesn't matter what you pick.

DR. KRULEWITCH: We do, do postmarket inspections; so we do, do site inspections, randomly, on studies that we are overseeing in the postmarket realm, as well as we do premarket. So yeah, and we would be in there, we would be looking at records and data and monitoring all of the records at whatever sites that we do inspections, just as we do premarket. So the answer to that is yes.

In addition, in every annual report, I can tell you that as an epidemiologist reviews that report, they review it extremely carefully, and if they don't have their answers met, then we will continue to ask questions and ask questions until we get all of the answers to the questions so that the data makes sense to us. And you have an epidemiologist going through each word in that report with a fine-tooth comb.

And then there are a series of management reviews over that review, so there are several sets of eyes that do look at that to make sure that the data is making sense to us. So there are two kind of safeguards in that sense, to answer the question that you're asking.

Most certainly, things can get through; most certainly, we can miss things as well as anybody else. I can't speak to what was presented here. We were actually, for one of those, trying to see if we had a sense of what might have happened and get a sense -- and sometimes I think if a patient is not getting response back or doesn't feel that they're getting called

back once they've had an implant removal, for an example, it may not truly be the case that they have been deleted from the study. That data may still be there.

And so does that answer your question?

DR. LEITCH: Yeah. And I guess the other thing is the -- you know, whether the sponsor -- you know, the idea of the sponsor communicating to the patient versus the PI at the local site is sort of another thing which is sort of unusual, that, you know, if the patient had issues, that those would be communicated to the PI at the local site, who would then deal with that and any complications that are reported should be in the forms that then go to the sponsor, and then your data, safety, and monitoring committee, you know, vets that periodically.

So it seems like maybe the sponsor is having a role that, you know, where they're more in direct contact with, potentially, with the patient, which could limit the patient's privacy, whereas the PI who is their operating physician already has that relationship.

DR. KRULEWITCH: Generally, it is the physician, so I'm not quite sure. I'll have to go and double-check on the protocol as to what was supposed to happen. But, generally, the scenario you've described is the one that we normally see where it would be that the patient would be responding to their physician. The physician would be reporting their concern to the sponsor; it isn't generally the other way that you heard it. So we can double-

check that, but you're absolutely right, and as far as confidentiality, that does maintain and protect confidentiality in a better way.

DR. LEITCH: The data that goes to the sponsor is de-identified from the patient.

DR. HENNESSY: Sean Hennessy.

For studies where the follow-up is going to be long-term and people's interaction with a surgeon is usually short-term, I don't see a reason why the primary interaction needs to continue to be with the surgeon or the surgeon's office. Couldn't that be handed off to a centralized research group who could continue that longitudinal follow-up with the patient, most of which or possibly all of which doesn't need to be face to face? It could be either via telephone, mail, electronic.

I don't see that there's a need to have surgeons and surgeons' offices continue to be involved in the follow-up of patients for a study that's going to last for a decade.

DR. KRULEWITCH: I think that that's a really good statement, and it's an important consideration. And I think that also is part of what we want to hear in our discussions.

And I think it does vary from study design to study design as to how that's set up. There are many places where there is essential data monitoring group or a data center that will collect data from a number of sites and manage sites. So it does depend on that.

But I think I would also recommend saving that, as well, for discussion because it is an important point, and I don't want it to get lost.

DR. LoCICERO: We're now beginning to get these wonderful points of discussion, so it tells me that the Panel is ready to start deliberating on the questions. So if you don't mind, if the Panel agrees, I'd like to ask one more question. Okay.

MS. DUBLER: Because I'm feeling very uncomfortable about going into this next phase in the following way, I think I'm not behaving, I'm not thinking I'm behaving like a nice guest.

So when we were invited to this panel, my thought was that we were invited to review the work that was -- that the two companies had agreed to present to us on their postmarketing studies, and I thought that was pretty nifty and let's see what it says.

The problem is that as the afternoon has gone on, the lines of authority and responsibility seem, to me, to be blurred, at least in my own mind, between the companies and their studies on the one hand and the FDA authority and how it's been exercised on the other.

So the loss to follow-up is so enormous that it's like ignoring the elephant at the dining room table, and that's something, it would seem to me, that perhaps the FDA should have had a prior position on or action, or perhaps this is all what the Panel is here to look at.

But, again, I'm not totally clear on lines of authority and

responsibility in overseeing studies between the sponsors on the one hand and the FDA supervisory structure on the other, and that makes comment from me more complicated. So at points when it's relevant, I think it would help me to understand more about that relationship.

DR. LoCICERO: All right, who wants to tackle that one?

DR. KRULEWITCH: I think we're waiting and we're confirming over there.

DR. MARINAC-DABIC: All right, so let me try to say again that -- and again, Dr. Krulewitch, I believe, was supposed to be also giving an overview before the Panel -- the actually, the Panel deliberations begins, about what FDA has done so far in order to improve the follow-up rates.

So just to kind of restate again that the perception that, you know, the FDA was just reviewing these reports without really engaging the company in, you know, tackling some of these issues, you will be reassured by hearing these slides or seeing these slides that there was a process that we follow. And I think because of the proximity of this Panel, we certainly would like to use this opportunity to actually hear from the Panel what the Panel thought of these strategies.

So if I may suggest that we have this brief presentation, actually just one or two slides, I believe, and then after that's looked at, you know, if you have any additional questions, we can go back to the FDA authority.

DR. KRULEWITCH: Before I start, I want to turn the podium over to Dr. Phyllis Silverman, who is one of our team leader statisticians because she has a comment about the follow-up rate as well.

DR. SILVERMAN: One thing that's not obviously clear is that although 35 percent loss over 10 years may sound huge to you, in order to end up with that, you have to follow 95.8 percent of the remaining cohort every year. If you follow 95.8 percent of the remaining cohort every year and raise that to the tenth power and then subtract 1, you'll end up with approximately either 35 or 65, I forget if it's -- 65. You'll end up with approximately 65 percent of the original cohort left at 10 years.

Now, if you want to have 80 percent of the cohort left at 10 years, you would have to follow about 98 percent of the remaining cohort at each of those annual follow-ups, and that's a very high bar to meet, and that's one of the reasons that we, when we design these studies, we thought that 65 percent follow-up at 10 years was acceptable because it meant following of about, you know, on average, 95 percent of the patients at each remaining year.

DR. LoCICERO: Okay, Mr. Halpin has one question.

MR. HALPIN: Today I heard a lot about the postapproval studies being investigational and a lot about them not being reimbursed, particularly in terms of all of this. And I wanted to get a perspective from the FDA for the Panel in terms of when you design a postapproval study, is the

purpose of it to be investigational and in this particular case, or to be looking at real-world experiences and collecting more data?

And is it your expectation that typically, when you design these studies, that there wouldn't be a situation where people could not get reimbursed or whether there's this huge burden of cost that seems to not belong to anybody, as is happening in this study? And I just wanted to get a general perspective as a starting point for our discussions later on.

DR. KRULEWITCH: I think this may be a special case because it's a cosmetic procedure, and this is something that is often faced by many of the members of this Panel because there are many cosmetic procedures considered.

With other procedures, oftentimes healthcare is reimbursed, so this question doesn't come up. The device is approved. These are postmarket studies after device approval, after reasonable assurance of safety and effectiveness. They are a condition of the approval; they are an expectation that the studies will be carried out.

So I don't know if that answers your question.

MR. HALPIN: The intent would be that -- was approved and normally you wouldn't consider that there would be a lot of reimbursement hurdles involved in trying to accomplish it. It was maybe one-off because of the nature of the product.

DR. KRULEWITCH: Correct. Because it would not be an

investigational study. This is only for approved devices as intended for use. Were it to be anything else, then it would become an investigational study, and it would not be part of a condition of approval.

DR. LoCICERO: Okay, I want the entire Panel to be happy with proceeding, so Ms. Dubler, are you convinced at this point, or do you have any further questions?

MS. DUBLER: I'll be quiet.

DR. KRULEWITCH: Okay.

Before I start, I just wanted to respond to Dr. Connor's question earlier about the remaining number of subjects that hadn't hit the window for Allergan and Mentor, because I have that.

For the two years for Allergan, we had 545 out of the 41,342 patients at the end of Year 2. However, there were 29,797, about 72 percent, that had not gotten to the window yet based on our 2010 annual report.

Additionally for Mentor, there was 19,349 of the 41,419 at three years and 22,078 of them, about 53 percent, had not gotten to the window yet.

I just wanted to make sure to answer that question because I have it, so --

DR. LoCICERO: Okay, great. I think we are now ready to proceed with the questions. For those Panel members who haven't found it, it's in the blue panel folder.

DR. KRULEWITCH: Well, before the questions, I want to -- I've got five slides of a little bit of summary and also to discuss what we've already done because it will add to the discussion. And I'll go through these rather quickly.

So first of all, just a little bit of summary once again. And I think I lost -- there they are. Just to update, we found similar patterns. This you've already heard. The only new safety concern is ALCL. We've had extensive discussion and concerns about the low follow-up rates, and there's variation in reporting and design, so comparisons are limited between the studies.

But the one thing that we wanted to point out is that when we hit the enrollment challenges -- which remember enrollment is now closed, but there was a period of time where we were seeing a lag in enrollment because we had a goal and they weren't meeting that goal as far as timeline -- we did work with both Mentor and Allergan.

Mentor, at that time, changed from their mandatory enrollment to voluntary enrollment. Allergan had four study protocols that they consolidated into one study protocol with related forms. And we reviewed and approved these changes, and it did improve, and we did get enrollment completed.

When it came to us noticing that there was low follow-up, we also worked with the companies, and we encouraged them to come up with

some ideas as to what they could do.

With Allergan, they came up with more frequent contact with study participants, they increased the incentive to study participants and conducted the focus groups where they came up with some answers and made some changes.

With Mentor, we worked with them to send out letters, which they referred to in their presentation, and we received 470 communications from the 40,000 letters that were sent out. The majority of these, they wanted to participate and they just had some questions for us and wanted some advice, and some of them had already completed their follow-up and they just wanted to let us know about that.

So we did identify some of the reasons for the follow-up, and Mentor did change their website. And we worked extensively in an interactive fashion with them to achieve these changes. But regrettably, we see that still the follow-up is still fairly low and the impact has not changed.

So we're still having discussions with them and trying to come up with some other ideas, and part of the reason we're here today is to talk about some of those ideas as well.

So when we think about the rest of this day and tomorrow, we want considerations to be taken for different possible retention strategies that may occur that we can now go from Year 5, or Year 2 and 3, actually, for the studies to the future, including maybe contacting other physicians and

involving them, primary care physicians, OBGYNs, or even other novel patient reporting mechanisms like social networks, which are now a new approach to maintaining contact with patients.

And as we've discussed -- and we hope to hear more discussion about leveraging data from existing registries outside the United States to answer some of those hard-to-answer questions on the rare events -- the Bayesian or statistical simulation models, powering the study for the more common endpoints and looking at it in a different light, and using other methodologies to detect rare events like we are doing with the registry for ALCL.

So that being said, I'm going to switch to the first question, and we'll have some discussion on that and we'll see how far we get today and then we'll continue after, I believe, public comment in the morning, I think, from the way that we have it set up in the agenda for tomorrow.

So the first question, which you can see here is that given the status of the current clinical postapproval studies, both the core and large, and the challenges that have been encountered in both enrollment and long-term follow-up, please discuss: (a) whether you agree with FDA's future considerations, which I just presented on the last slide; (b) what changes, if any, do you think we should make now to the postapproval studies that are in existence today? (c) And please talk about that 35 percent over 10-year loss to follow-up rate.

DR. LoCICERO: Okay, thank you.

Just in terms of tomorrow's agenda, the agenda that was distributed is incorrect. The open public hearing will be first tomorrow morning followed by the continuation of the questions. So that -- whatever was sent out was wrong, so we'll be doing the open public hearing first in the morning.

Hopefully, we'll get through at least Question 1 this evening and then move on from there. So I'd like to begin.

Does anybody have any openings? Okay. Dr. Glassman.

DR. GLASSMAN: Len Glassman.

If I could take (c) and then (b). (c), I think, is very reasonable. My big concern is if (c) is reasonable, (b) is a disaster. That is, I don't think that either of the studies that we heard this morning made me comfortable that the data, that the conclusions, are necessarily valid. We are missing so many patients, and whether by design or by accident, those may be the patients that had problems that didn't get reported. We don't know.

We heard anecdotal evidence from patients and patients' representatives this afternoon, some of which suggested that it was not represented in the data, which bothers me. So I'm real uncomfortable that we have anything close to a valid set of conclusions in (b) based on what (c) should be and what reality was.

DR. LoCICERO: So who are the stakeholders in this

information? Is it the companies that we're holding responsible here alone? Is it the physicians as well? Is it the patient, physician, and company? Give me some feelings about that.

Dr. Connor.

DR. CONNOR: I think that's why I asked what the consequence was. I mean, it seems like if we really want to improve (b), you know, we tell Mentor make it better or your product is off the market. And I'm not saying we should do that, but that would make the rate get better for sure, and that's why I wondered, you know, what sort of legal standing FDA had to actually make that claim because, you know, Allergan talked a lot about incentivizing patients and trying to figure it out. And I think that that's very good that they're thinking about that, but it seems like incentivizing the companies is, you know, and letting them know what the consequence is would be the key to increasing these rates.

DR. LoCICERO: Going back to the old Harvard Business School thing, you can have a kick in the ass and it can either be a positive kick in the ass or a negative kick in the ass, and you're describing a negative kick in the ass. Is there a positive kick in the ass that we can give?

DR. CONNOR: I mean, right now their, you know, product is being sold and they're making a lot of money and, you know, it seems like most people are satisfied. That's good, but if there really are remaining questions, and apparently there are, that's why we're here, then getting the

numbers, which I think (c) is appropriate, it's just that we're not going to get there this way and it seems like some -- you know, drawing the leg-backs right now seems to be what we need to do, not necessarily that kick in the ass yet.

DR. LoCICERO: Dr. Leitch.

DR. LEITCH: Well, again, I think (c) is okay because what you're doing is you're designing the number of patients to start out with to end up with enough if you have a 35 percent dropout rate to answer the question, so that's okay, but again, they're way short of that at the present time, so that's the problem. And I guess I'm just surprised that there's not any evidence support for the physicians to administer the study.

You know, most clinical trials, you have to have some support to be able to run them at a local site, and you're asking, it sounds like most of these are in private practice where, you know, they don't have a clinical research office to help them administer the study, so you're essentially asking a physician's office to do work with no support. And, you know, if there were some support for doing the work, then it might be more likely to be accomplished.

I mean, even in clinical trials, which are imbursed at the NCI rate, which is a little bit higher than what should be for this, but that's still not enough, really, money to administer those studies. You know, I mean the sites struggle because they don't have enough support to administer the

studies at the local site, so I think that's something that needs to be considered in order to get you where you need to be.

And particularly, if they want to retrieve, you know, the patients that have already been entered in a trial, to retrieve them, that's going to take -- that is going to take work to do, and it really is the physicians that are going to need to do that or to get it initiated because they're the ones that own those patients and own their ID.

DR. LoCICERO: Dr. Honein and then Dr. Hennessy.

DR. HONEIN: So I think I agree with the others that (c) is a reasonable goal, but I guess the challenge I see is I'm not convinced that even the original enrollments at each of the two large PASs represent a sample that could be generalizable to the larger cohort of women who received implants.

So I think what's really needed is one well-designed PAS that's administered independently that gets both of the devices enrolled in it and properly incentivizes both the participants and the providers so that people are very motivated and there are checks along the way to make sure you're enrolling a representative sample and that your loss to follow-up is not overly biasing your results.

I mean, studies are tough, participation is very difficult to maintain, and people do have the right to withdraw. But I think it could be designed much better, and I guess I'm not very convinced that the current

studies are salvageable based on what we've heard today.

DR. LoCICERO: Dr. Hennessy.

DR. HENNESSY: So in our research design course that we have in our degree programs, we harp on the fact that you can't design a study until you know what the goals of the study are. I haven't heard it clearly articulated what the goals of the study are supposed to be. Is this supposed to be surveillance for unknown events, is this supposed to be to test specific hypotheses about specific events?

If you design one study to do everything, you're going to end up with a study that doesn't do anything well. I think we need to figure out what the goals of the study are before we can design it.

DR. LoCICERO: Okay. So that is a major question. So I guess we need to go back to the objectives in the protocols to see -- and the primary endpoint, if you wish to review that, maybe this evening. And we can discuss it again a little bit tomorrow because you're going to have to get back into your computer and plow through a lot of stuff to get there.

Yes?

DR. GALANDIUK: I agree with many of the comments made, and I agree with the 35 percent is appropriate, but I think the data that is presented is also not representative at all, and one of my concerns is, first of all, from a lot of the things that were reported in the public session is, it doesn't seem as if any of the patients had a number of an IRB to call. Even if

the study was done in private practices, there should have been a central IRB that was involved and patients should have had a resource number to call other than the company and other than the physician that was treating them, and that doesn't seem to have been the case.

Second is in my own practice, I take care of a lot of patients with Crohn's disease and ulcerative colitis, which are two autoimmune diseases, and many times these diseases manifest themselves only when the patients are in their twenties and thirties. In many cases, these patients already come in with implants in place, and I'm sure there are many other autoimmune disease conditions where they occur later and I'm very concerned -- I think it was Dr. Kimmick [sic] that was complaining about so many young women getting these implants before many of these diseases are apparent. And at least in my population, only one of five of those patients has a family history of these disorders.

So I think there's a very big need to assess on a wider population level what the true incidence of autoimmune diseases in these patients be, especially since in these studies that was excluded.

DR. LoCICERO: Dr. Vega.

DR. VEGA: The feeling that I got -- is that people felt alienated; they sort of felt left out to dry. I think that if you've had breast cancer as I have had several times, what you get very, very, very upset about initially is that your body somehow has betrayed you and turned against you. And you

look to help, you look for help.

And I think that when people are looking for help and they're grasping at whatever they can get -- and I heard that clearly today -- and they don't get a phone call back, a personal phone call, and they don't get some kind of feeling that somebody is on their team, and I can understand that you can't do a rah-rah for 40,000 people, I'm clear about that, but there has to be a way that they can link up to either people who have been in the same situation or in a more positive situation, some kind of feeling that there's a continuity. It really has to be, because psychologically, I think we're playing with fire; I really mean that.

I administer, for my HIV and breast cancer patients, it's a very, very easy clinical, it's an exam for depression screening; it's four questions that you can -- and then there's one on social isolation. It takes maybe six minutes, okay; I have it in English and Spanish. I think if people can feel that they were evaluated, let's say, on something very simple, even over the phone, and then maybe even suggested that they were referred to some place where they could seek help, I'm feeling that the study might do a lot better in terms of just on many multi-levels.

And I think that people here have expressed a sense of discomfort in many regards, but for me, particularly, I don't feel there's a big connect between the emotional expectations and ultimately the process. Something in the process has broken down; that's what I believe.

DR. LoCICERO: So in addition to those -- which are wonderful. Dr. Hennessy was talking about having maybe another group coming in at maybe two years or something and then following for the remainder of that portion. I'd like to hear from the surgeons what their feelings are concerning that particular approach.

Dr. Leitch.

DR. LEITCH: Well, you know, while I think it would be ideal if surgeons were following these patients, because I think some of the nuances of local complications are going to be best ascertained by a surgeon, some of these other things, you know, which is -- you know, this other issue about the rare conditions, those could be identified by a primary physician and could be a way of getting follow-up.

And the prevention trials did use that methodology of, you know, if the patient had seen a gynecologist, even if they didn't see the PI during the study, that you would get the data from the gynecologist, so I think some of these systemic issues could be picked up by a regular physician.

But, again, to get the data from that regular physician, you have to give that person some support to get it, you know. I mean, you can't expect somebody who knows nothing about the study all of a sudden to be giving data and you get consent for and all these kinds of things to accomplish that. But, again, if the sponsor would be willing to work on that issue, that would be -- you know, that would be another methodology in order to

accomplish it.

But I think if anybody's having an issue that's identified, either in the questionnaires and they need to get, you know, back to the surgeon to actually do an exam and confirm what the findings are and be prepared to respond to that and report that.

DR. LoCICERO: Dr. Mount.

DR. MOUNT: This is a very confusing question on multiple aspects, and I want to even just step back and just look more globally at really what we're trying to accomplish with a PAS study anyway. I've heard some people say oh, well, you know, this would be a clinical trial and things like this. This is completely different than premarket approval. So there's no randomization; there is no ability to randomize. All of these patients have had the treatment.

So the PAS studies, in my mind, and correct if I'm wrong, are really to cast a wide net to see if there are some unusual things that are coming up or unusual design flaws in the implant or unusual systematic issues. And so it really can't be designed with the same sort of statistical power or expectations as a premarket approval study.

For my own, you know, for answering these questions, is it appropriate to assume a loss of a follow-up rate of 35 percent? It really does go into who is the stakeholder. Ultimately, the stakeholder is ultimately the person who has the foreign body in their chest obviously. The younger

generation -- and I've heard this many times in my practice -- really have a core feeling that these are very safe, and they also have a core feeling that a lot of the extra studies, a lot of extra things, are just busy work on our part and I am sure -- or maybe I shouldn't say I'm sure because I haven't done a study, but I'm leaning towards the reason for the lack of follow-up or interest in that stakeholder group in particular is because they don 't perceive a problem with it and we're really asking for a lot of extra things to be done.

What I think makes more sense -- so the follow-up rate of 35 percent, I think, is superfluous. How many questionnaire studies do we see that get published with 50 percent response rates? You know, and that goes into standard literature. So I don't know that I could actually give a number on what I feel like a normal follow-up rate is because I don't think that the study should be designed in this way.

This is just throwing something out there, but with so many patients being at so many different times in their healing process and late-term and all this, to me it seems like more valuable information could be randomized in such an assay such as a snapshot type of interview or survey, meaning that you take all, you know, the 30,000 women that have had -- or 300,000 women that have had breast implants in the time period that we have collected so far, and then randomly and statistically significant power to know the number of people to get, randomly select those patients for a particular snapshot and ask them the questions that they need to be asked to

get the answers to your questions.

And then secondly, I think that the -- at least, in my mind, the reporting agencies where particular patients that are having troubles, that are feeling yucky after having something, can report this, that can actually drive the questions that are asked at the specific snapshot time for a wide net, for a wide casting sort of interview or physical examination or whatever, and I think that that randomization will take care of a lot of the bias for people that may self-select to either be in the study or be out of the study, and with potential serial times and examination. I think we could get a lot of data in this wide-cast net that we're really looking for, that the particular way that this study is currently set up won't give us the information.

DR. LoCICERO: Dr. McGrath.

DR. MCGRATH: I'm going to go back to your original question, and that was that Dr. Hennessy had suggested that maybe an outside party rather than plastic surgeons be doing the follow-up. I would make two comments about that.

First, in terms of good patient care, the plastic surgeon is clearly the best person because there is no group in medicine that knows more about breast implants than plastic surgeons, and as much as endocrinologists and rheumatologists know, not all of them do. I mean, some really are not familiar with this issue at all. And, therefore, the group that really follows this very closely and lives this is plastic surgery, so the patient

who is having an untoward symptom is best off sharing this with a plastic surgeon.

However, for the purpose -- leave that aside. That's patient care. I think that's a patient care piece. I mean, primary care doctors could be educated, but it would be a massive undertaking to bring them up to speed -- to know what to look for, in other words.

Now, let's go to the study thing. I don't see any reason why it couldn't be a designated outside party as an investigator seeing the patients, which is, I think, what Dr. Hennessy suggested when he originally made this idea, that perhaps the follow-up would be to capture these people by an outside designee at intervals rather than trying to drive everybody back to the original surgeon or to try to respond to the manufacturer. And I think that's something that is a technique that we could certainly talk about more.

Before I finish, though, I want to say one thing for those of you who have never been involved in this type of panel before, and that is, it's very good to hear the patients' input, but we have to remember that the patients who spoke today are very polarized people, and many of these have implants that date back to manufacturers that aren't in the business anymore, that were covered with products like polyurethane that hasn't been around for 25 years.

And I was struck that only a smaller proportion of them were patients who were actually in these studies with more current events going

on, which almost begins to suggest that maybe we're doing a better job at keeping those people informed and involved, considering that, you know, now we're doing 250,000 of these a year and yet we don't find a lot of people bubbling up with these problems who are coming here to talk to the FDA, who were treated within the past five, seven, or 10 years, or rather way back in the distant past when the situation was different.

So I think that those of you who aren't in patient care need to understand that I don't think there's an iceberg that was exposed by the testimony today; I think it's very good for you to hear it, but I think that I'm getting a sense that there's some undue alarm arising that we actually don't see in clinical care with these products at the present time.

DR. LoCICERO: Dr. Hennessy.

DR. HENNESSY: So in terms of follow-up, the usual clinical trial model is that patients continue to go back to the provider that entered them, and that full-court press kind of approach could work here for common events that need that kind of evaluation, but if you're going to be enrolling thousands or tens of thousands of patients, that's simply not feasible for those numbers.

Another approach is to have multiple study arms, depending on the aim, so some people will get closer follow-up with the surgeons. Other people will have periodic contact via telephone, e-mail, regular mail, and then when they report adverse medical events, then the idea is to get medical

records associated with those events to validate and adjudicate those.

Follow-up would also need to be done with the National Death Index so that we know when individuals die. It would be ideal to try to get their insurance information and have follow-up. That way, people are going to have so many different insurances and they're going to change so frequently over time that I think that that's probably not feasible.

DR. LoCICERO: Ms. Dubler.

MS. DUBLER: We're talking about this study as if it's a regular clinical study passed by an IRB with a DSMB. I'm not sure, from what we heard this morning, that that's the case. So it sounds to me, from this morning, that these are company initiatives. I would be somewhat surprised if they were passed by an IRB, but happy if they were. I see heads nodding, so they were passed by an IRB, good. Which has a role in administering them?

(No response.)

MS. DUBLER: No.

DR. LoCICERO: Usually not.

MS. DUBLER: So the notion that -- there's a basic conflict at the core of the study, which is yes, it's true that you may join and you're free to leave at any time. I mean, that's the ethic of clinical research, right? And yes, that really undercuts the ability of the companies to do the studies and get the data in a way that we want.

So as one of the authors of the Ethics Regulation of Research with Human Subjects, when finding a very peculiar problem, you look for a creative solution, and that solution would be a dialogue with patients who came into the study about how important it is for them to stay in and what incentives they'll have. And the reason I say that, and I come back to Dr. Hennessy's point about a lack of clarity on the endpoints of the study, and I have a feeling that's because the endpoint of the study is really to see whether these things are safe and effective.

So even though I am suggesting that the prior advisory group suggested to the FDA that they were and the FDA has, in fact, declared that they are safe and effective, which is what I think is affecting young women who think they're being bothered for no reason -- I mean, these are safe and effective; go away. But I think the importance of the postmarketing studies was because there is some uncertainty about this. And the quality of the data that we're really looking for is to whether these are safe and effective, and that creates a great deal of confusion in discussion.

DR. LoCICERO: And one of the things is going to be the cost of the MRI, which we're going to get to next after Dr. Connor.

DR. CONNOR: So regarding being a change, I think, you know, one key thing I would like to see is maybe a mailing that would go out to all patients and try to track everyone down, to give them, you know, maybe a new point of contact.

It sounds like some people, you know, maybe Mrs. Dorsey, you know, went to her plastic surgeon and that surgeon said oh, these autoimmune things, it's not caused by this and they aren't receptive. Or they went to the company and the company wasn't receptive, but I'm sure, you know, the legal teams of some of these companies won't let the company write back to them, you know, even if, you know, the altruistic scientist, I've seen that happen.

So it would seem like with the FDA communication, maybe there should be a third party entity that says, you know, even if we think we haven't heard from you so you're living happily ever after, that people keep getting mailings to just say if you have one of these things, here is the person to contact.

And also, I think, I would like to ask -- and this speaks to one in maybe three later, but I wanted to bring this up tonight -- is given a concern is we're measuring specific things, but it's not measuring what patients are -- some patients are complaining about, whether it's possible for both companies to provide to us tomorrow morning, like the CRF patients get every -- because we have the protocol, but we don't -- I haven't seen what patients get asked every year. So maybe if Mentor and Allergan can provide us copies of that in the morning, that would be good.

DR. LoCICERO: I think that would be very helpful for us to see.

So now, you know, we haven't talked about it much, but what

kind of participation do you think we'd have if we took the cost of the MRI out of this? Anybody want to take that on?

DR. CONNOR: It sounds like patients are still concerned or don't understand that MRI is non-ionizing or non-radiation, you know, giving, so that seems like --

DR. LoCICERO: Yes?

DR. HONEIN: So is the question someone else reimbursing the MRI or no longer recommending the MRI?

DR. LoCICERO: Let's say they were free in Guatemala and everybody would go to Guatemala and get one. I don't want to say Mexico. Okay, Puerto Rico would be good.

DR. HENNESSY: So I'm not sure I understand the purpose of or the goal of having periodic monitoring with MRIs. Is that a stated goal of the study? We know that the MRIs aren't 100 percent sensitive, they aren't 100 percent specific, they aren't even recommended in other countries. If the goal is to do a naturalistic study, what happens in the real world, then women will either get MRIs or they won't and either eventually will get identified or they won't.

So I don't think it makes sense to -- I don't know whether it makes sense or not, but I haven't heard a rationale for having MRIs be part of a naturalistic study when we know that they're not happening in real life.

DR. LoCICERO: So there are just a couple of us who were here

at the meeting where there was recommendation for that, and so maybe it would be better if Mr. Melkerson would just talk about the rationale for adding the MR to the studies.

MR. MELKERSON: I wasn't at the meeting, but the rationale behind the MRI issue was twofold, and we keep hearing about rupture being the issue. One of the questions that the large postapproval studies we're trying to -- if silicone leaks or escapes the shell, the question was, was there or was there not an association with connective tissue diseases or other things, so if you didn't know the device was ruptured, you couldn't necessarily correlate signs or symptoms to a connective tissue disease.

So part of the reason for the MRI was the -- and at the time, ultrasound and other techniques were not deemed to be as good as MRI. We've heard today that there may be some other techniques now, but they didn't exist or weren't as predictive five or six years ago. So the issue with the MRI -- and you've described this a natural history study or that's not what we do in practice -- typically, studies are not what we do in practice because we're trying to answer a question that we do not know the answer to and the objectives behind -- and I just pulled up the objectives from one of the postapproval studies -- was to compare to national norms the occurrence rate of these signs and symptoms of CTDs to the patient populations that had received the breast implants.

So when you're asking about objectives for the MRI, it was

twofold. It wasn't just to detect whether or not the device broke. What we were understanding from -- and you've heard that in the testimonies today, that the device, after the fact, was found to have been leaking. So the question is what happens with that material. Does it or does it not have a correlation or connection to the connective tissue diseases?

DR. HENNESSY: I think we found that large -- it's going to be difficult if not impossible to get large numbers of women in a study where they have periodic MRIs. You could do that with small numbers of women. Doing that with thousands and tens of thousands of women, I don't think is a feasible objective.

DR. LoCICERO: Dr. Glassman.

DR. GLASSMAN: Len Glassman.

Couple of things have changed, I think, in the last five or six years, and if I say something really stupid, will my plastic surgery colleagues throw something at me and shut me up, but one of the things we worried about a while ago was connective tissue disease and unsuspected rupture. You couldn't correlate connective tissue disease with silicone gel rupture unless you knew that the implant was ruptured.

So one of the reasons, I assume, for that was to find out whether the implant was ruptured. There are a couple problems with that. One is the problem with gel bleed. In other words, some silicone gets out of at least older implants without an actual rupture; it gets to the outside. The

other is we don't know that it's not the shell rather than the silicone gel that is causing connective tissue disease if there is, in fact, a link that we don't know.

Given we don't believe that there's a link and given that most -- and here's where I'm really going to get in trouble -- most plastic surgeons probably would not explant a pure intracapsular rupture with no symptoms, maybe we don't need the MR anymore.

DR. LoCICERO: Dr. Galandiuk.

DR. GALANDIUK: I was just thinking you might have the data already on the patients who have undergone reconstruction and are getting MRIs anyhow. For example, what Dr. Duda was describing in her practice, if we just analyze the data on those women, they might not be truly representative of the augmentation, but at least it's data that's already in hand that we could look at.

DR. LoCICERO: All right, let me try to just summarize where we stand at the moment to focus us because we're starting to kind of wander.

So I think everybody seems to agree that the goal of 35 percent over 10 years is a reasonable one for this sort of study and that there doesn't seem to be a lot of disagreement at that. And that we've suggested a whole lot of changes, including potentially changing the way the patients are followed, the questionnaires that are being used, the groups that are being analyzed.

The data gatherer and then maybe considering our biggest problem or what has -- at least the surgeons, during the open public hearing were saying, was the issue which is the disincentive because the MRI cost money. It wasn't necessarily what we heard from the patients, but it was what we heard from the physicians who are involved in the studies.

So additional points. Dr. Leitch.

DR. LEITCH: Well, I don't think the MRI is the disincentive for participation in the study because they don't have to get it, you know; what they have to do is show up for their visits and answer the questionnaires. The MRIs, they would like to have that done, and what I understood from, I believe, Allergan was that what they were looking at with respect to the MRI was did people comply with that recommendation, which is in the labeling, which goes to whether it's reasonable to continue having the labeling in a certain way if nobody ever does it, if it's unreasonable expectation to do.

So while you can get some of those other things that we're talking about -- about, you know, how often does it predict it, how often is it right, you know, those kinds of things you can get out of that data. And when you're looking at real-world application, one issue is do people get it and do people who have a rupture, how is it first identified, is it identified by symptoms or is it identified by the fact that they got an MRI done at a certain interval of time?

And so I think that's what's being looked at with respect to the

MRI, and I don't think that's really the reason patients don't participate because they can always say no to the MRI without being "thrown out of the study."

DR. LoCICERO: Any other points? Yes.

MS. CROUCH: It's really not about the MRI, but one of the things that concerns me is are we really looking for potentially some genetic component? So are there a subset of patients that are genetically predisposed to having these connective tissue disorders?

I'm thinking of the ALCL, which is immune-mediated, the connective tissue disorders, and are we collecting enough information to be able to look at patients that may be at greater risk that we can then pass on in the future?

We know that there are a lot of rare adverse drug events that are genetically determined, and I just wonder if there is some sort of genetic determination here, and are we collecting enough information to be able to make that determination?

DR. LoCICERO: I'd like to hear from the patient advocates, if they see a way to increase accrual.

MS. MATTIVI: I don't know about that, but I do agree with the point that was made that I think the compliance with the MRI recommendation is a slightly different issue than compliance with follow-up over a 10-year period. I think those are two very different things that we're

looking at.

DR. LoCICERO: Dr. Whorton.

DR. WHORTON: Elbert Whorton.

Let me see if I ask the question correct. Do you believe without the MRI there would be sufficient signs, symptoms, complications that are measured in other ways to assist and effectively look at the safety and the efficacy without the MRI?

And, secondly, are there people that have dropped out of the study, dropped out of follow-up, that have the complications that we would no longer get to look at in terms of those kinds of signs and symptoms?

So I don't have a problem with 35 percent. I have a problem with the 65 percent and how reasonable and representative it is of what they're trying to look at. If all the complicated cases went away, then the 35 percent may contain that, and that concerns me a lot.

DR. LoCICERO: Ms. Dubler.

MS. DUBLER: I was just wondering, in your summary, whether you thought that summary of points argued for an emendation and tinkering with the present existing studies or whether your summary was directed at a notion of new studies to be created?

DR. LoCICERO: This is in response to Question 1, which is about the current study, so -- and I'm just trying to summarize for everyone. I'm not trying to de novo develop new thought here. My job as chair is to channel

you, so -- and that's sometimes tough for everybody.

But, anyway, does anybody have additional comments about the directions of the current study and the suggestions for how to improve those? Yes.

DR. GALANDIUK: Actually, one study -- one of the comments that was made about the MedWatch by one of the people in the public session. I was looking on my computer on the MedWatch site, and I found it extremely difficult to negotiate. And if I were a patient, I think I would have a hard time filling out a report on that.

So one of the things that I think it should be easier for patients even not participating in the trial to report something, and there should be easier -- I don't know if FDA has a Facebook page for MedWatch or some very easy way that patients can report adverse events. I don't know, IRB always tells us to do things in fifth grade language and make it extremely easy, and I don't perceive it to be that.

DR. LoCICERO: Mr. Halpin.

MR. HALPIN: In looking at the study and trying to execute a study of this size, you've got what looks to be a thousand sites, probably at least double the number of investigators, 40,000 patients being followed for 10 years. I think that the ability of any one sponsor to do a study of that size has to be somewhat limited and, you know -- so on a go-forward basis, I would think that if you've already achieved an approval based on the core

study data, that there might be ways to do a broader collection of data that's not as intense as this is.

I don't know whether you drop some of the study endpoints or drop some of the time visits, but having all these healthy people walk in all the time, you really have to incentivize them, you've got to have staff and structure in place, and you have to really remind them a lot. And I think if you get to this size, and I'm not sure it's within the scope of any one sponsor to really execute this study over a 13- or 14-year time period successfully, so I'm thinking maybe just practicality.

DR. LoCICERO: Dr. Vega.

DR. VEGA: I was thinking that there are patient navigators and that what we talked about before, translating, that might take a broader scope for translation and that might mean that you could have people who, maybe, are volunteers, who have been through the process. I call them comadre, which means significant other person that you identify with, but you can call them a lot of things, patient navigator, where somebody can call because it's really awesome.

I looked at the site, and I'm saying to myself, well, maybe it's because I'm getting old or whatever, but it's a lot of stuff to go through, so having some kind of a helping hand might be really a very important piece to getting the things done more readily. I agree with my colleagues.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: I was wondering, Dr. LoCicero, if we shouldn't talk a little more about incentivization, specifically financial incentivization, because there really are three issues that have kind of bubbled up in the conversation today.

One would be bias that could be introduced; another would be effects. I'd like Dr. Duda to comment on that. The other, if we're talking 80,000 people, would be cost, and maybe Mr. Halpin could make a comment about that.

But I think we should talk a little bit about this because we keep mentioning it, but we probably should explore it a little bit.

DR. LoCICERO: So, again, this is the issue we were talking about before about incentive, and you can have positive incentive, negative incentive, or altruistic incentive, and so we need to sort of discuss that maybe as the final piece to Question 1.

MS. DUBLER: I think it's hard to think about. It's perhaps unfair to think about negative incentives for patients. I can't imagine that that would not be an undue exercise of a vulnerable population.

On the other hand, as I said about six hours earlier, I'm perfectly willing to consider negative incentives for physicians. I'm not sure what would work. I remember when we first started doing a big, hospital-wide palliative care study and one of the PIs said that she was working on the "break the kneecap" theory of incentive, that she was going to get people's

attention.

Maybe, if you don't get follow-up on your patients, you don't get the product to use. I don't know how to do this. I have been impressed by the huge task that was approved for these companies when, again, I don't see the infrastructure, I don't see the supervision, I don't see all the pieces that I'm used to seeing. But I do see physicians in private practice, and I think they are the ones to be in touch with their patients and get their cooperation.

And these are not researchers and they don't have a research nurse and, therefore, there's got to be some serious liability for them in not proceeding to get these data. And, again, I do think that despite the fact that they've been declared safe and effective, I think we're still looking for those data. So I don't know how we get the attention of the physicians to do the task, but I think it's appropriate to think about some rather serious interventions.

DR. MCGRATH: I think what I was wondering more was paying people to -- you know, paying either patients or doctors, and I wanted to explore the ramifications of that because everyone questioned the physician who did have a payment scheme for his patients rather closely, and did anyone have concerns about bias or ethics of that type of an arrangement, either for the physician or for the patient? And I just thought that would be a worthwhile topic for us to look at.

MS. DUBLER: Just to begin it, I don't have concerns at all about

payment for these physicians and these patients in this situation. There's a rather extensive literature on paying very poor -- there are two issues that are raised. If you're in a very poor neighborhood, where many research institutions are, and you dangle $1,000 in front of a very poor person, that may be a sufficient amount of money to get them to ignore or set aside values that might preclude them from participating in the research.

The second issue is contingent payment where you say well, we'll give you $1,000 after your ten visits, but we won't give you anything if you don't get to your tenth visit. And there's a pretty big discussion in the ethics literature that that does feel unfair.

In general, payment -- and the person who has written most widely about this is Christine Grady, who is at the Clinical Ethics Center at the NIH -- and in most cases, payment is evaluated by a patient the way other data are evaluated by patients, so in general, I think payment, if it's going to work, is a terrific idea.

DR. LoCICERO: Mr. Halpin.

MR. HALPIN: Just to speak a little bit to the cost issue. If you look at the core study in the compliance with that versus the postapproval study, there's a clear delta there, and a lot of that is because for a core study, you're going to make sure that those sites have the infrastructure to do the research. And I think, in looking at past studies with implants, I've seen postmarket approval studies that are 5,000 implants or 5,000 patients, and I

think sponsors can get their hands around that.

If you start to get to 10,000, you start to talk about registries or overall exposure where people are independently reporting into registries. You start to get to 40,000, and you're in unmarked territory. And I think what may have happened is we may have reached the point where, you know, maybe we get more value out of a 5,000-patient postmarket approval study or a 10,000-patient registry versus a 40,000 or 80,000-patient approval study because it may just not be doable, at least from a cost point of view.

DR. LoCICERO: Okay, yes.

DR. HONEIN: I think the literature does support that providing incentives to the patients, and likely for the providers, too, although I'm less familiar with that literature, does work and does improve participation pretty dramatically.

And I think what the sponsor said about the focus group suggesting that that wasn't a big factor, that is what we tend to hear in focus groups, yet when we provide incentives, we get higher participation, and I think you get a more representative participation because certainly there is a core group that is much more motivated and much more altruistic who will participate, regardless.

And I think, similar to the divergence that's seen with the reconstruction patients versus the augmentation patients, but I think appropriate, non-coercive-level incentives are important in today's busy

world to actually get people to participate, as you're asking them to use their time.

DR. LoCICERO: Dr. Hennessy.

DR. HENNESSY: So the augmentation patients don't see themselves as patients. They have their implant, and then they go along with their life and they're people; they're not patients. I don't think you're going to be able to pay them the amount that they would need to go visit a physician for a reason that they want it for the next 10 years.

I just don't think that that's a feasible expectation, that the contact with the individuals, at least, in the augmentation group is going to have to be direct via some centralized contract research organization or university, and it has to be as non-invasive as possible from the perspective of the participants with appropriate follow-up when they identify an adverse event, but that's going to be very rare. These are healthy young women, and they're going to have very low event rates, and they're not going to be used to being medicalized.

DR. LoCICERO: Okay, let me try to summarize what we've done up to this point.

Now, in addition to the summary that I had, we talked about the MR maybe being a much smaller study or maybe we have enough data already and that might be able to come out. We discussed the issue of positive incentive for the patients, potentially negative incentive. Positive

incentive, also, maybe for the physician in terms of data collection. Negative incentive for the physicians about maybe not being able to have access to product and negative incentive for the company, including the big one, which we've danced around a little bit.

Any additional comments?

DR. MOUNT: Del Mount.

I do have significant concerns about the potential of reducing availability of a product to various physicians whose patients either choose not to or don't complete the study. I think that there's a lot of ethical concerns about that, and I think that it really reduces, ultimately, the patients' choices of who they choose as their physician if they select to have a silicone breast implant and the physician they want to place it has been "negatively impacted" and told that they cannot use this product, which I think is unenforceable, anyway. I think that that really limits patients' choice, and I think that it really borderlines on antitrust. So I would not really think that that would be a great idea, to disincentivize by limiting product to physicians that place breast implants if their patients choose not to participate. But I'm not an attorney.

DR. LoCICERO: Dr. Galandiuk.

DR. GALANDIUK: Just had a comment on the MRI. Before some individuals were talking about the superiority of the high-resolution ultrasound. I can't conceive that that's going to be a realistic replacement,

for ultrasound, because I don't think most plastic surgeons would be doing ultrasound in their office on a regular enough basis to be very proficient at it.

Correct me if I'm wrong, from the plastic surgeons in the office, but is that something that most plastic surgeons would be doing regularly?

DR. MCGRATH: Some of the ones working in the breast centers do, but it's possible that people who aren't doing breast cancer patients probably aren't, but it's not -- you know, it would involve a training process.

DR. LoCICERO: Dr. Glassman.

DR. GLASSMAN: Yeah, breast ultrasound is a lot more difficult than it looks. I've tried to train ER doctors to do simple ER ultrasound, and it's uniformly fine when it's normal, and when it's abnormal, they usually miss it, but thank God for CT scans. In radiology centers, most breast ultrasound is done by technologists. In surgical offices, it's done by surgeons.

I'm going to get in a lot of trouble, but neither one is typically the best-qualified person to do it. And you can only see the front of the implant clearly. The back wall is mostly invisible, certainly from -- we saw a very pretty picture on the screen of a little break in an anterior wall. Well, only what, a third of the implant breaks, a third of the surface is on the front? You can't see it in the other places. So it's not a credible replacement for MR.

DR. LoCICERO: Okay, any additional comments?

(No response.)

DR. LoCICERO: Dr. Marinac-Dabic, have we answered your

questions concerning Question 1?

DR. MARINAC-DABIC: Things that I wanted to, again, stress. If you can elaborate a little bit more about what other changes, you know, can be made. For example, there had been discussion about, you know, improving the infrastructure of the sides or any additional monitoring requirements or things like that. I know this had been captured in the discussion, but it would be also beneficial if it's captured, also, in the conclusion.

DR. LoCICERO: Okay. So this would be increasing infrastructure, which will also increase cost, and I assume that that would be to the sponsor.

So any comments concerning increasing infrastructure to capture data? Dr. Glassman.

DR. GLASSMAN: Len Glassman.

Question for the statisticians. If someone has missed several appointments in the protocol and they can be re-found now, can we use that data or are we past the point and we really need a new protocol?

DR. CONNOR: Use them if you re-find them.

UNIDENTIFIED SPEAKER: Use your microphones, please.

DR. LoCICERO: Well, let me just summarize. Yes, it's possible that data will be usable and welcomed, I take it.

Yes?

DR. CALLAHAN: This isn't to that point, but I felt the point about the genetic information was very important, and particularly thinking in terms of genetic environmental interactions, and maybe it's not relevant to Question 1 about changes, but if it is relevant, what was the summary on that?

DR. LoCICERO: I think we can come to that in another question.

Yes, Dr. Honein.

DR. HONEIN: I just wondered about the possibility of the patients who currently haven't been meeting the schedule, of offering the opportunity for them either to rejoin the full protocol or to rejoin for a final evaluation at least, so maybe some participants that aren't willing to sign on for the 10 years might be willing to sign on for one more data collection point to at least evaluate who you're losing and how they're doing at the point you're losing them. I know there's always a tradeoff --

DR. LoCICERO: You're talking about maybe an exit interview?

DR. HONEIN: So, you know, where you have the Mentor study where 80 percent of the people are gone, could you reach out to that 80 percent and see if some subset was willing to at least come in one more time even if they're no longer willing to join the full protocol.

DR. LoCICERO: And then maybe one more data point but then an exit interview to find out why they left and how it could be improved in the future.

Yes?

MS. DUBLER: I want to come back to some of the points that Dr. Hennessy raised about the basic structure of this protocol and ask the statisticians whether there is some way of statistically sampling your larger cohort to get you to a number that might be feasible for the companies to approach and keep in a study for 10 years. Or whether the endpoints that we've identified absolutely require the huge number of patients that are now the goal.

DR. CONNOR: Yes. And to answer that, I think the key is, you know, because we're looking for really rare events, we need 40,000 people because we only have, you know, a couple percent or even less than a percent had these events.

So if we were sure that the people we track were the people having the events, that's, you know, more acceptable, but, of course, we don't know that, especially hearing things, what are patients feeling. They're no longer welcome because they're not good patients, and if that's more commonplace, that's a big problem, which is why tracking the 40,000 is more important.

DR. LoCICERO: So maybe to just expand infrastructure a little bit here. Another approach might be registries or maybe empowering some patient advocacy groups to try to bring these people in.

Any thoughts about how we can -- we're going to hear again

tomorrow from a number of organizations. How can those individuals, other than coming to a meeting every five years, be empowered to assist in the collection of data of these kinds of individuals?

DR. MCGRATH: Well, just in terms of the professional groups, you're right. I think we're going to hear from some things that certainly the American Society of Plastic Surgeons has done with databasing.

But I think that another issue, though, with trying to harness perhaps consumer groups, we've got to go back to the privacy issue. And patients may voluntarily choose to go in to a consumer group, but I think there are issues with asking our patients to join a consumer group if they have privacy concerns.

DR. LoCICERO: I didn't -- wasn't -- my suggestion was sort of thinking using the group, using a consumer group, to encourage patients to return to follow-up.

DR. MCGRATH: Yeah, but then they'd have to know who they are and who's going to tell them. I mean, again, you have a privacy issue because a lot of our patients really feel strongly about privacy with regard, really, for reconstruction and augmentation. Despite the fact that many don't, there are a huge number that do.

DR. LoCICERO: But are there ways that they can do it generically?

DR. LEITCH: The question is whether their constituency are the

people that have breast implants and, you know, now made some pretty pointed comments about how research should document all this stuff, about what they do to promote women to participate to do that, and if the women who get breast implants aren't in their constituency, then they're not going to have any force of action.

But if they felt strongly about it, then they should advocate in other venues rather than a small meeting like this. It should be in a more public advocacy for all women who have breast implants to participate in clinical trials, you know, that sort of an advocacy. But I don't think you see that very much promoted by organizations. Currently, anyway.

DR. LoCICERO: Please.

DR. GALANDIUK: Yeah, Susan Galandiuk.

You might get somebody like Susan Komen, just through their breast cancer interest, promote patients to answer, participate in a trial with respect to the reconstruction.

DR. LEITCH: That's the easiest group to work with. I mean, you've already seen it in the trial, that they are the ones that show up for follow-up and certainly as a group are highly motivated to participation in clinical trials, have interest in these issues, you know, didn't "pick it," you know, they didn't want to have breast cancer, but now they're in that boat and they're having to do it. And certainly right now, there's a trend towards more bilateral mastectomies.

In other words, more aggressive surgery, which requires -- well, ideally requires reconstruction, and so it is, perhaps, more a bigger issue now for breast cancer patients than it was when we were sort of in the heyday of breast conservation. Over the last 10 years, there's been a big swing towards bilateral mastectomies, and so this is an issue, and creative ways of reconstruction is this is something patients are very interested in, so that would be a population who would likely participate with, you know, less "incentive" stuff.

I mean, they would showing up anyway for appointments and -- but you would have to have the infrastructure, again, you know, in terms of if they're followed primarily in their surgical oncologist's office or their medical oncologist's office as opposed to the plastic surgeon, that there would need to be some support for those offices to gather the data.

DR. LoCICERO: So one organization is Lamaze, that's actually already a partner in MedWatch, and I don't know anything about that organization or whether they're speaking tomorrow, but would it be possible to harness something like that group to encourage participation in a generic way?

Yes.

DR. MOUNT: Del Mount.

The ASPS website is a very high-traffic website both for patients getting information about procedures, as well as even finding physicians that

perform certain procedures, geographically, you know, subspecialty-wise and all. And, you know, I think that both ASAPS as well as ASPS could really help or partner with us as far as just even advertising, you know, oh hey, you know, did you get your breast implant registry updated or have you sent information in, and maybe even adding, you know, some direct links from that site because it is such a high-traffic site. I think that would be a really great way to partner with them in particular.

DR. LoCICERO: So, Dr. Marinac-Dabic, we've addressed a couple of issues in terms of infrastructure and suggested a few more approaches. Is this sufficient for Question 1?

DR. MARINAC-DABIC: Yes, it is. Thank you.

DR. LoCICERO: Thank you.

So we are reaching our witching hour for today. I'm afraid to begin another question at this time, but it's been a productive day, and I'm hoping that we'll be able to continue in the same productive manner tomorrow morning, which is to begin at eight o'clock. Thank you.

(Whereupon, at 6:20 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

GENERAL AND PLASTIC SURGERY DEVICES PANEL

August 30, 2011

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

_____

CATHY BELKA

Official Reporter

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947